MAY 1954

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles

by

K. M. BRINKHOUS

LOUIS R. WASSERMAN

HYPERTENSIVE VASCULAR DISEASE

Transcription of a Panel Meeting

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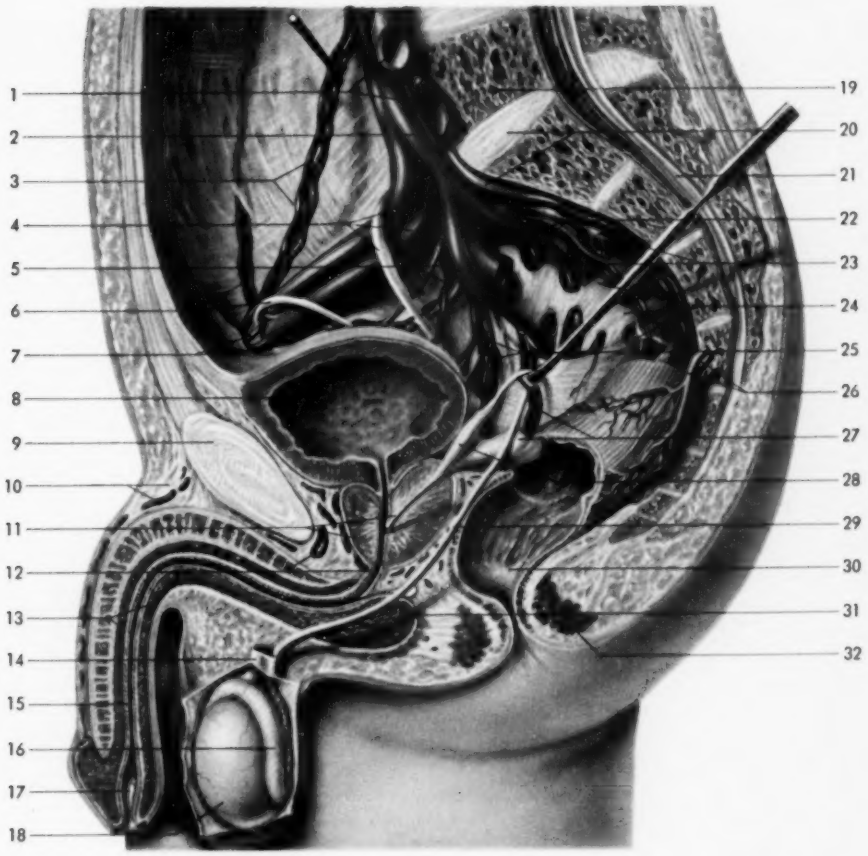

1 Common iliac artery and vein
2 Internal iliac (hypogastric) artery
3 Spermatic artery and vein
4 Ureter; external iliac artery and vein
5 Superior vesical artery and vein
6 Deep iliac circumflex artery and vein; right ductus deferens
7 Inferior epigastric artery and vein
8 Urinary bladder
9 Symphysis pubis
10 Fundiform ligament of penis; superficial dorsal vein of penis
11 Prostate gland; ejaculatory duct
12 Deep dorsal vein of penis; prostatic urethra
13 Corpus cavernosum
14 Spermatic cord (cut)
15 Cavernous urethra
16 Epididymis
17 Navicular fossa
18 Testis
19 Fifth lumbar vertebra
20 Middle sacral artery; intervertebral fibrocartilage
21 Vertebral canal
22 Lumbosacral trunk; superior gluteal artery
23 Lateral sacral artery; sympathetic trunk ganglion
24 Sacral nerves; coccygeus muscle
25 Inferior vesical artery and vein
26 Superior hemorrhoidal artery and vein
27 Seminal vesicles; middle hemorrhoidal artery and vein
28 Ampulla of ductus deferens
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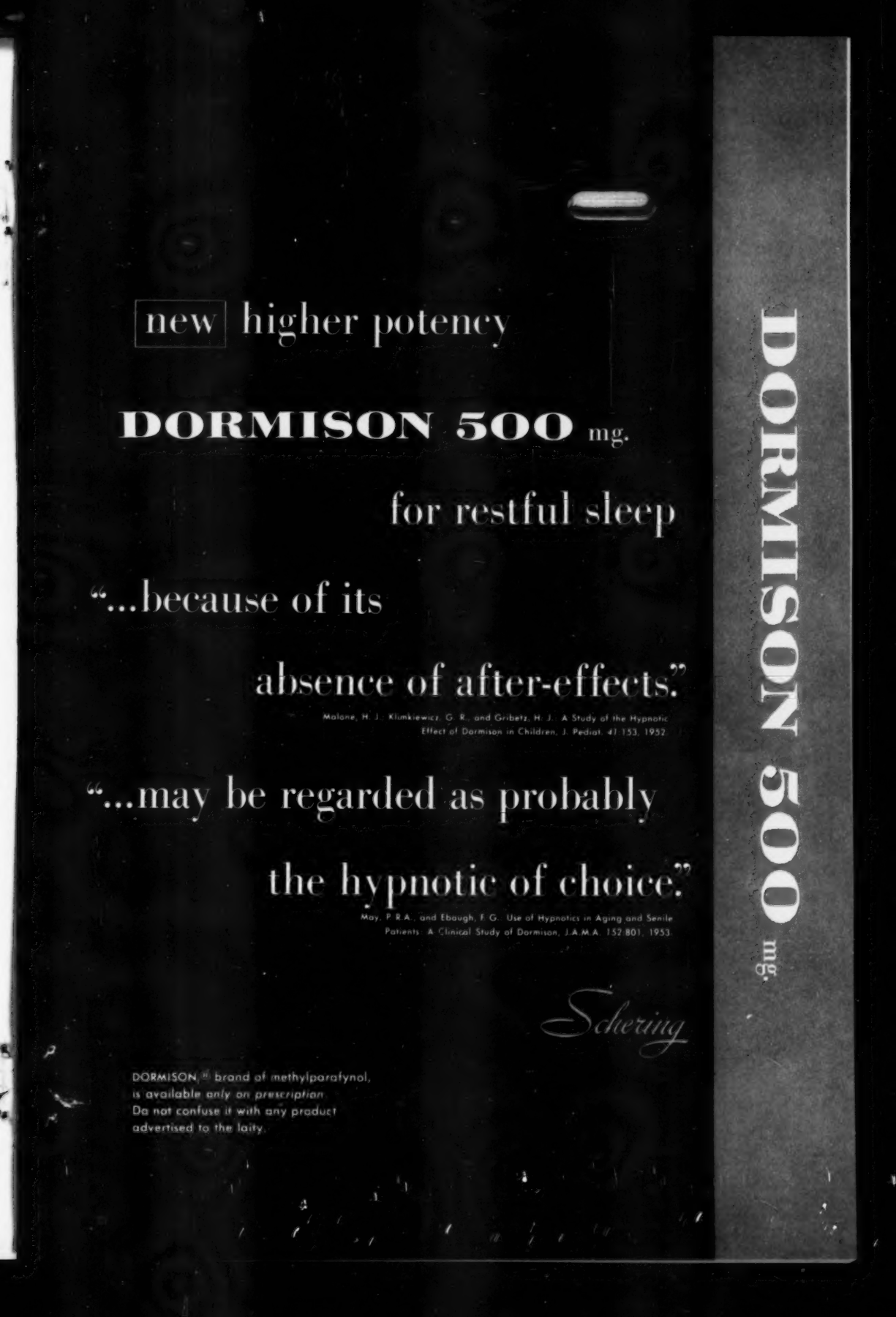
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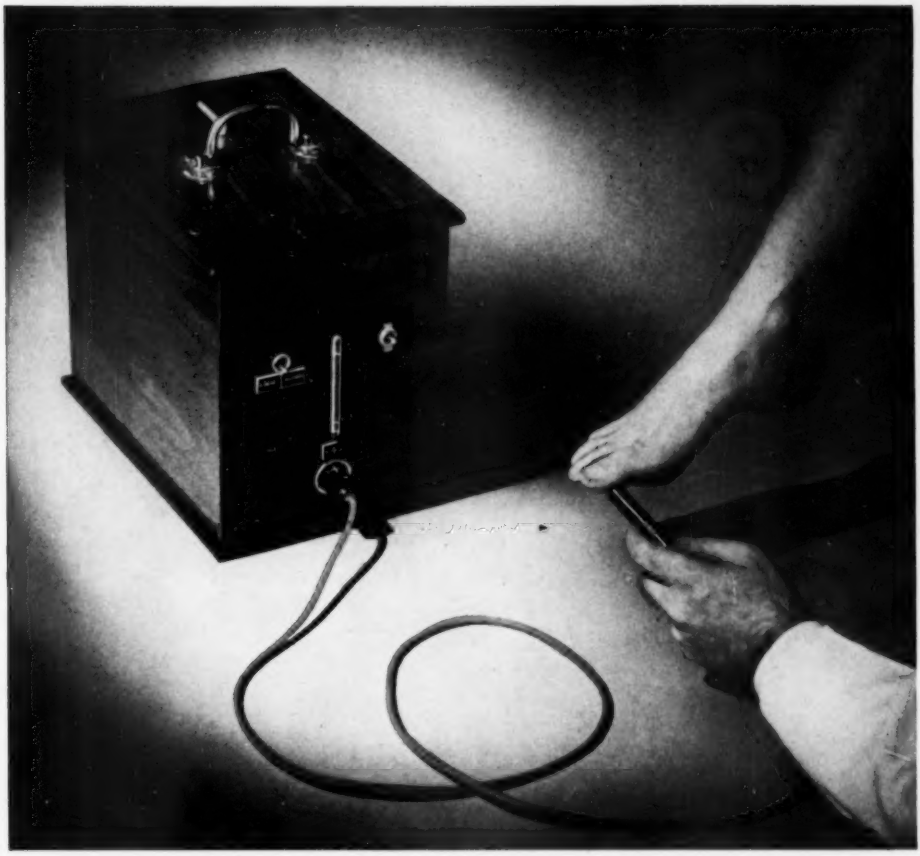

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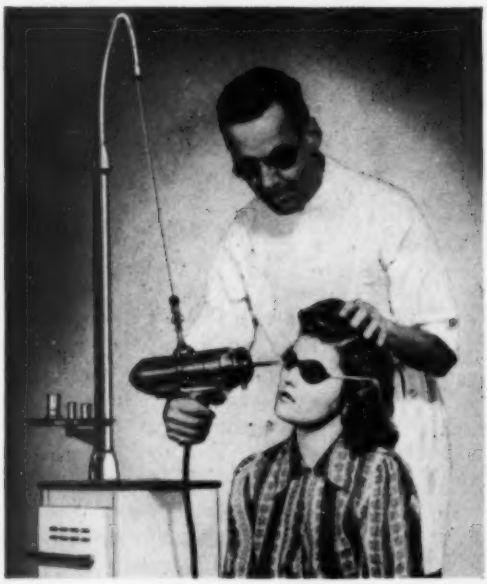

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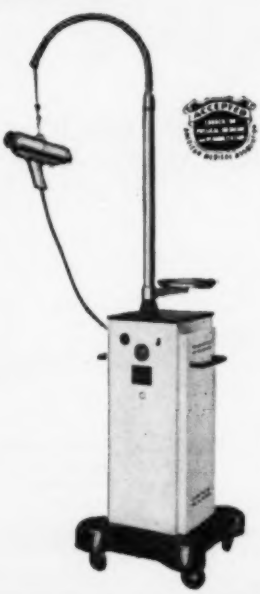

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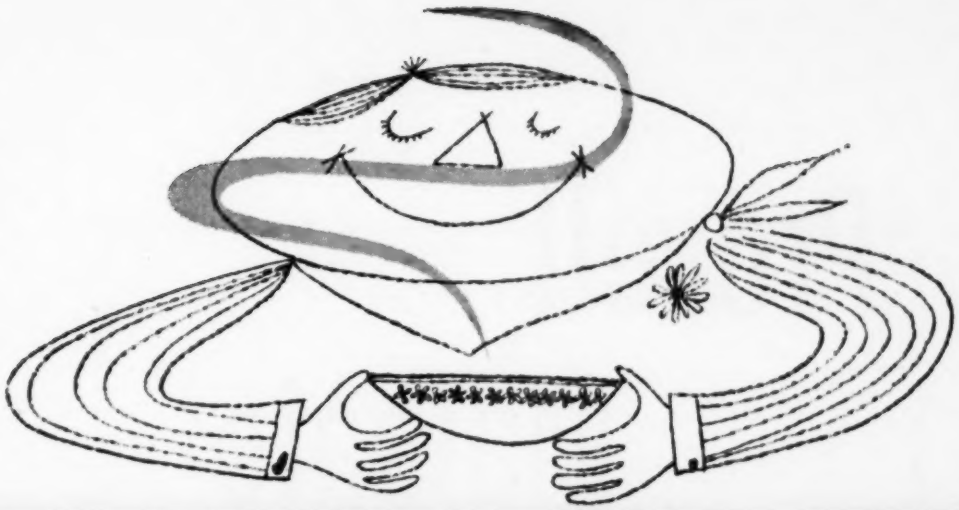

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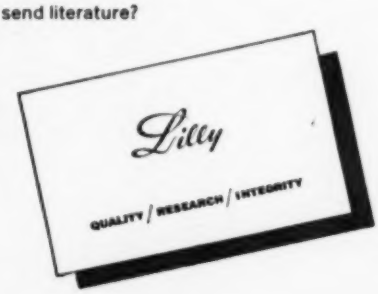

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ROBERT L. CRAIG, *Editor*

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BULLETIN OF
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VOL. 30, NO. 5 MAY 1954

HEMOPHILIA*

K. M. BRINKHOUS

Professor of Pathology, School of Medicine, University of North Carolina, Chapel Hill, N. C.

FIFTEEN years ago Dr. William H. Howell addressed the Eleventh Graduate Fortnight on this same topic, hemophilia.[1] It might be well to recall briefly the status of investigations on this disease a decade and a half ago, as presented by Dr. Howell. He indicated that the disease is an inherited tendency in males to bleed. The mode of inheritance appeared to be sex-linked and recessive, but studies were incomplete. The basis of the bleeding tendency was not well understood. Some writers still emphasized a vascular abnormality. Dr. Howell had first thought an inherent defect in platelets existed, but from his most recent experiments he concluded that there was a plasma deficiency of a soluble thromboplastin. By thromboplastin he meant simply a substance which accelerated thrombin formation. He pointed out the difficulties in diagnosis and the limitations of the clotting time test. For therapy whole blood transfusions were recommended. He propounded many questions, most of which cannot yet be answered: 1) Are platelets needed for the action of plasma thromboplastin? 2) What is the exact

* Presented at the 26th Graduate Fortnight of The New York Academy of Medicine, October 23, 1953.

role of this factor in the clotting process? 3) What is the source of this factor in the body?

Today most students of hemophilia agree with Howell's view that a deficiency of a specific plasma procoagulant exists. A few, however, believe that an excessive amount of a plasma anticoagulant, possibly antithromboplastin, is responsible for the defective clotting.[2, 3] This aspect of hemophilia, as well as many others,[4] cannot be adequately treated in a limited time.

Tonight I would like to present the results of some of our studies on three main phases of the disease: 1) the inheritance; 2) the clotting defect and its correction; and 3) some aspects of diagnosis and treatment.

Inheritance

Our studies on inheritance have been carried out not only on human hemophilia, but also on an identical disease in dogs. Before considering these genetic studies, I would like to describe briefly the canine bleeding disease.

About six years ago we had the good fortune to be directed to a kennel where it was observed that roughly half of the male pups of certain mothers had a fatal disease characterized by peculiar joint swellings. Initially diagnosed as rickets, there was no improvement with cod liver oil or calcium. The recognition of abnormal bleeding, and the presence of the disease only in males and only in the litters of certain bitches, led to the determination of the clotting time and the correct diagnosis of hemophilia. Apparently a mutation had occurred.[5] We obtained the female transmitters of this disease early in 1947 and have been studying their descendants since that time. The commonest manifestation of the hemorrhagic tendency is a chronic recurring hemarthrosis, most severe in the large joints. Subcutaneous hematomas are also common. Fatal exsanguination from hematomas occurring in the chest wall and in the mediastinum has been frequent. Other sites of fatal hemorrhage have been the gastrointestinal tract, and occasionally the pleural cavities and the brain. The clotting defect in these animals is indistinguishable from that in human hemophilia. Unless controlled by transfusions with normal blood or plasma the animals practically always die from massive hemorrhage during the first few weeks of life.[6]

As in human hemophilia, the canine disease appears to be inherited as a sex-linked recessive characteristic. The gene responsible for this

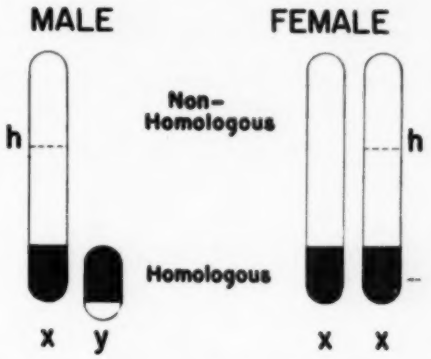

Figure 1—Diagram illustrating location of hemophilic gene, *h*, on non-homologous portion of X-chromosome.

pattern of inheritance is located on the X-chromosome (Figure 1). In the male, this chromosome is paired with the shorter Y-chromosome. The gene site for hemophilia is diagrammatically indicated by the letter *h*, located on the unpaired, or non-homologous segment of the chromosome. Such an affected male is called a hemizygote. In the female, with two X-chromosomes, the gene for hemophilia is paired with a normal allele, *H*, not shown in the Figure. Such a female, normal except that she may transmit the disease, is the heterozygote.

To indicate the pattern of our genetic studies in canine hemophilia, the possible matings in a sex-linked type of inheritance are outlined in Table I. Some thirty other conditions besides hemophilia are inherited in this same manner.[7] The most common mating in hemophilia, the heterozygous female (xX) and the normal male (XY), is shown in line 2 of the Table. The symbol "x" indicates the chromosome with the affected gene for hemophilia. It will be recalled that, with reduction-division in the formation of germ cells, all ova have X-chromosomes, while sperm are of two types, those with an X and those with a Y chromosome. The heterozygous female, with one affected x has two types of ova, one with a normal X, the other an affected x. Thus, on mating to a normal male (XY), two types of female offspring, normal (XX) and heterozygous (xX), and two types of male progeny, normal (XY) and hemizygous (xY), are expected. The most famous human mating of this

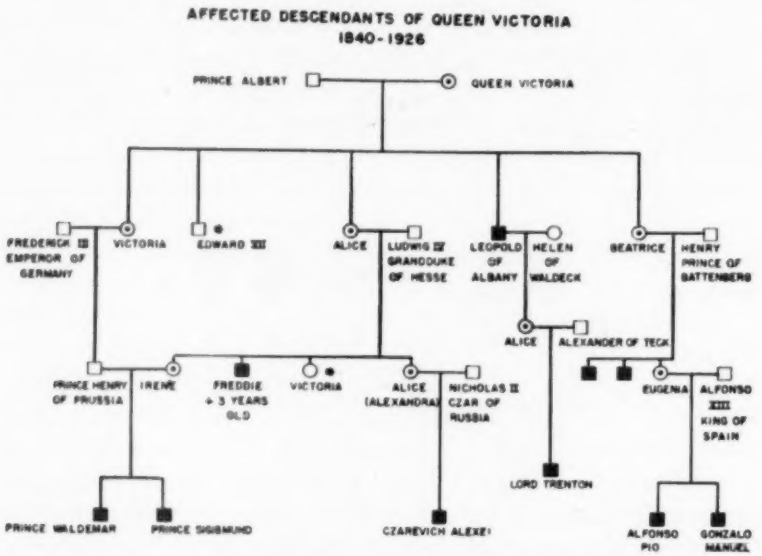

Figure 2—Hemophilia in descendants of Queen Victoria; partial pedigree. Solid square represents hemophilic male, dot in circle heterozygous female.

type is undoubtedly that of Queen Victoria (xX) and Prince Albert (XY). From this union there were three heterozygous daughters and one hemophilic son (Figure 2).[8] Incidentally, the present House of Mountbatten, as pointed out by Iltis, originated by a union of two unaffected lines of Victoria's descendants, indicated by an asterisk in the Figure. In all, up to 1926, there were at least ten hemophiliacs in this pedigree, the most famous of which was the Czarevitch Alexei.

In our hemophilic animals, the matings first studied were of this same type, xX-XY. The result of one such mating is shown in Table I. There were ten puppies in the litter; three of the five males were hemophiliacs, and three of the five females were heterozygotes. This is very close to the expected ratio of 1:1:1:1. The heterozygous state was demonstrated only by breeding and examination of the litters for hemophilia. This limitation has made our study a most expensive and time-consuming one.

A test of the cross, hemophilic male (xY) with normal female (XX), became possible after we succeeded in raising bleeders to maturity by

TABLE I—MATINGS IN SEX-LINKED TYPE OF INHERITANCE GENOTYPES*, EXPECTED AND ACTUAL, CANINE HEMOPHILIA

	Mating		*Genotypes of Progeny*									
			Expected (Ratio)					*Found (Actual Numbers)*				
			Males		*Females*			*Males*		*Females*		
	Sire	*Dam*	XY	xY	XX	xX	xx	XY	xY	XX	xX	xx
1.	XY	XX	1	—	1	—	—	—	—	—	—	—
2.	XY	xX	1	1	1	1	—	2	3	2	3	—
3.	xY	XX	1	—	—	1	—	3	—	—	1	—
4.	xY	xX	1	1	—	1	1	2	2	—	1	1
5	XY	xx	—	1	—	1	—	—	1	—	4	—
6.	xY	xx	—	1	—	—	1	—	4	—	—	4

* X = chromosome with *H* gene; x = chromosome with *h* gene; xY = hemizygous male; xX = heterozygous female; xx = homozygous female.

repeated administration of plasma transfusions. One of these males is now over five years of age. He has sired over 250 progeny, over a 100 of which have been hemophiliacs. In the mating shown in the Table (line 3) this bleeder male was the sire. The three male pups were all normal, as they received their X-chromosome from their mother who was normal. The only female that lived proved, on breeding, to be a heterozygote. We had thus duplicated in the first part of this study the matings reported in human hemophilia up to that time, 1948.

We next tried the mating, the heterozygous female (xX) and the hemophilic male (xY), shown in line 4. This mating has been the subject of much debate in the older literature. The theory calls for half of the males being hemophiliacs and half of the females being heterozygotes. The other half of the females should have both X-chromosomes affected—homozygotes (xx). It had been postulated that such a combination is lethal and it would not be possible for such a female to exist. The outcome of this mating in our dogs was thus of great interest. It is seen in the Table that the males were distributed according to theory, two being hemophiliacs and two normal. One of the females was a bleeder, indistinguishable as far as the clotting defect was concerned from the bleeder male siblings.[9] The other female, we have found out just recently by breeding, is a heterozygote. Since this demonstration of a female hemophiliac in dogs in 1949, there have been reports in the British literature of seemingly bona fide female hemophilia in humans.[10, 11]

Having determined that the hemophiliac female can actually occur, we then concentrated our attention on raising these animals. Our aim now was to test the two possible crosses with the hemophilic female. The results of a cross between a hemophilic female (xx) and a normal male (XY) are shown on line 5 of the Table. Only one male in this litter was tested and as was to be expected, he was a hemophiliac since he received his X-chromosome from his mother. The four females were all non-bleeders, and on testing for heterozygosity, all had hemophiliac offspring.

The other mating, a hemizygote (xY) with a homozygote (xx), is shown in line 6 of the Table. All of the offspring, both male and female, were hemophiliacs.[12] Thus, all of the possible crosses in hemophilia were tested, and in all cases, the results indicate the inheritance is sex-linked and recessive. A double dose of the gene, *h*, in the female is no more deleterious than is the single dose in the male. Further discussion of the genetics of this disease will be deferred until after some aspects of the clotting defect have been considered.

The Clotting Defect in Hemophilia

It has been generally recognized for many years that the prolonged clotting time in hemophilia is reduced to nearly normal after transfusions with normal blood or plasma. As the clotting time becomes normal, hemostasis also approaches normal. This response is illustrated in a twenty year old male hemophilic patient, who was prepared for a tooth extraction by a 300 ml. whole blood transfusion. The clotting time dropped from two and a half hours to nine minutes. Except for the usual small amount of bleeding immediately after extraction, no continued bleeding developed until five hours later. Then, oozing from the extraction site began. This is a frequent characteristic of hemophilic bleeding, and is called the rebleeding phenomenon. Hemorrhage continued for nearly ninety hours in spite of daily transfusions. During this period the clotting time fluctuated from normal or nearly normal values immediately after transfusion, to prolonged times of eighteen to seventy minutes twelve to twenty-four hours later. This hemorrhage stopped, however, when transfusions of only 100-200 ml. were given at frequent intervals of five to ten hours, to keep the clotting time within or near the normal range (nine to thirteen minutes) all the time.

Another characteristic of the clotting defect, observed in 1939,[13] is

the persistence of high prothrombin levels in serum after clotting. In normal blood, it had been shown previously that prothrombin disappeared rapidly after clotting, with only traces remaining after three hours.[14] In hemophilia, on the other hand, there was no detectable loss in one hour, and even after nine hours, roughly 90 per cent remained. After transfusion of a hemophiliac, prothrombin is utilized quickly, almost at the normal rate.[6, 13] Thus, there is a block in the reaction in which prothrombin is converted to thrombin. This block is removed by normal blood. In Howell's terms, the normal blood furnished a thromboplastin for the hemophilic blood.

Next, a test was made of the question: Is the beneficial effect of normal blood due solely to the plasma, or are platelets also necessary? This test became technically possible with the introduction of silicone-treated surfaces in blood clotting. It was found that normal plasma, essentially platelet-free, was just as effective as platelet-rich plasma or whole blood in correcting the prolonged clotting of whole hemophilic blood.[15] Thus, platelets, at least from a normal individual, are not required. A parallel experiment was then done, using a hemophilic plasma practically platelet-free, instead of whole hemophilic blood. No clotting occurred on adding platelet-free normal plasma, but prompt clotting occurred with addition of platelet-rich normal plasma or whole blood. Thus, platelets, either normal or hemophilic, appear to be necessary in addition to normal plasma to correct the hemophilic defect. It was concluded that hemophilic blood is lacking in a plasma component, antihemophilic factor (AHF), which requires platelets to make thromboplastin available. Two separate hypotheses were proposed about this time as to the mechanism of this reaction. One, very tentative, suggested that AHF was necessary to lyse the platelets and thus make platelet thromboplastin available.[15] Data to substantiate this have not been obtained. Another hypothesis, by Quick,[16] turned this around. He suggested that platelets liberate an enzyme which activates the antihemophilic factor. This view has been retracted recently.[17]

To study this problem further it was necessary to devise a measuring stick for the antihemophilic factor. The development of such an assay procedure proved to be a problem of considerable magnitude. After three years of patient labor with several associates and a number of medical students, we believe we have at least two separate and fairly accurate gauges for this clotting factor.[18, 19]

The basis of the first of these AHF assay methods[18] will be outlined briefly. It was pointed out that little or no prothrombin is utilized in clotting hemophilic blood over a period of several hours. On the addition of small graded amounts of normal plasma or plasma fractions with antihemophilic activity, there is progressive increase in the rate of prothrombin utilization, until the hemophilic blood contains approximately 1 per cent of normal plasma. Then prothrombin disappears at almost the same rate as in normal blood. In this range (0-1 per cent) of added AHF, the residual prothrombin of hemophilic blood becomes an index of AHF. Remarkably small differences in AHF can be determined. Unfortunately this procedure is technically difficult and very laborious. For this reason we searched for a simpler method.

The second method[19] is based upon the observation that certain thromboplastins clot hemophilic plasma more slowly than they do normal plasma. We have called thromboplastins of this type, partial thromboplastins, and we have called the clotting time obtained with such thromboplastins, the *partial thromboplastin time*. On adding increasing amounts of AHF, either as normal plasma or plasma fractions, to hemophilic plasma, clotting of the mixtures with partial thromboplastins is accelerated. When the mixture contains the equivalent of 15 to 20 per cent of normal plasma, the partial thromboplastin time is very nearly the same as with normal plasma alone. With larger amounts of added normal plasma, there is little or no change in the partial thromboplastin time. By using the range of 0-10 per cent of added AHF, that is, the range in which greatest change in clotting time occurs with small increments of AHF, we have been able to assay this factor nearly as well as with our first assay procedure.

A number of studies were then made with the use of these assay procedures, in an attempt to obtain a better understanding of the nature of this plasma factor, its metabolism in the body, and how it interacts with other factors in the clotting mechanism. None of these studies are complete and all that can be done at the present time is to give a progress report of some aspects of these investigations.

The Nature of AHF. This clotting factor is associated with the euglobulins and fibrinogen in plasma. Thus, with precipitation of plasma proteins following one-fourth saturation with ammonium sulfate, nearly all of the AHF is precipitated.[19] It can also be separated from plasma by mild acidification, the AHF coming out with the proteins first precipi-

tated. It was also found to be somewhat concentrated in the plasma fraction I, precipitated in the cold with alcohol by Cohn's method. The material is heat labile, but can be separated from fibrinogen by judicious regulation of temperature.[20] In stored blood the AHF gradually disappears, although it is somewhat more stable than is often thought. For instance, well collected bank blood kept for one week under ordinary conditions with ACD preservative at 4° C., retains nearly all of its AHF activity. This clotting factor, along with fibrinogen and labile factor, remains in the plasma after adsorption with such reagents as barium sulfate[20] and calcium phosphate. AHF is inactivated by fibrinolysin, large amounts of thrombin and probably by other enzymes. It is adsorbed on some of the alkaline earths as kaolin but it is poorly eluted by the usual methods. In our laboratory AHF has been only partially purified; the best products are about 100 times more potent per mgm. of nitrogen than is native plasma. Since as little as 0.004 per cent of normal plasma in hemophilic plasma accelerates clotting, it can be concluded that less than 3 *ug* AHF per ml. is responsible for this effect.

Metabolic Studies of AHF. After intravenous administration to a hemophilic patient or animal,[6] AHF has been shown to be immediately effective. This effect can be followed by repeated determination of the prothrombin utilization rate, or by actual assay of AHF. Considerable loss of activity occurs early, but AHF activity, although much reduced, still persists for as long as 4-6 days. If data on hemophilic subjects are transferable to normal individuals, it would indicate AHF has a relatively short life span, the half-life being less than forty-eight hours.

A search has been made for possible sites of synthesis of this clotting factor. Since the liver appears to be concerned with fabrication of other clotting factors, the effect of $CHCl_3$-induced liver injury was studied. In such animals the prothrombin and fibrinogen promptly fell to low levels, but the AHF levels were unchanged.[18] Likewise, the AHF levels remained within normal limits following administration of antivitamin K compounds, such as dicoumarol.[18] Total body irradiation, which caused almost complete destruction of lymphoid tissue, did not affect AHF.[21] In these experiments on dogs, a marked thrombocytopenia and hemorrhagic tendency occurred. Prothrombin utilization was impaired, yet the AHF remained normal throughout. Splenectomy had no influence on AHF, either in the normal or hemophilic animals. Renal insufficiency produced by uranium nitrate likewise did not result in any change

in AHF. From these experiments we concluded tentatively that neither the liver nor the lymphoid tissue was responsible, at least in toto, for the manufacture of AHF. Also, that the deficient AHF in hemophilia is not due to abnormal renal permeability, with loss of the factor in the urine. Numerous other experiments have been performed, but in none of them has there developed evidence which would conclusively indicate the site(s) of origin of this clotting factor.

AHF in Clotting. Few critical data are available to indicate the place of AHF in the overall clotting reaction. It has been pointed out that platelets and AHF are both essential for clotting, and that they may participate in the same or closely related reactions. AHF disappears from blood as it clots.[20] After a short latent period, AHF gradually decreases, so that in ninety minutes very little AHF is left. Calcium appears necessary for this reaction. Traces of this factor may remain in serum for long periods, but there is little to substantiate the occasional old report that serum has a beneficial effect when transfused into hemophiliacs. The rate of loss of AHF from clotting blood has been used[12] as an index of the rate of clotting, similar to the prothrombin utilization test. AHF utilization parallels prothrombin utilization. This raised the question if they might disappear in the same reaction. We attempted to determine this by a mathematical analysis, comparing the rates of AHF and prothrombin utilization. The data themselves were not sufficiently critical to reach a conclusion.

Serum contains an accelerator factor(s) which appears to influence the utilization of AHF in clotting. The serum factor is probably the same one that Owren calls convertin, and Owen calls stable factor. It was found that in hemophilia an accelerator evolved in about the same amounts as in normal blood, although the rate of its formation appeared to lag somewhat. Addition of the serum accelerator (SA) to hemophilic blood failed to eliminate the block in prothrombin conversion, even though the clotting time was shortened.[22] This experiment is contrary to what one would expect, if one of the clotting theories in vogue today is correct; this theory states AHF and platelets form thromboplastin, which in turn activates proconvertin to convertin, and only then does prothrombin conversion occur.[23] Contrary to this theory, our data indicate that even with SA present, AHF is still needed. A synergism was found to exist between SA and AHF, however. With both present in hemophilic blood, prothrombin conversion proceeded more rapidly

than with added AHF alone. This is probably due to the abolition of the latent period by SA. The shortening of the clotting time of hemophilic blood with SA addition alone may mean that in hemophilia the AHF deficiency is not absolute; with a trace of AHF, SA eliminates the latent period and allows relatively prompt evolution of a trace of thrombin, which is responsible for the accelerated clotting.

While there are many such experiments dealing with limited aspects of AHF in relation to clotting, it is not yet possible to indicate its exact position in the overall clotting process. A relationship to platelets, prothrombin, and serum accelerator factor has been demonstrated. Many variables probably exist which are not yet recognized. For example, Sorbye's nutritional studies in the chick suggest there are many clotting factors still unrecognized.[24] In addition there are probably other reaction products, aside from thrombin and serum accelerator, which are active in clotting and which may be related to AHF.

Before going on to the question of the diagnosis and treatment of hemophilia in the human, I would like to refer to another animal hemophilia—swine hemophilia. Several years ago at the University of Missouri a hemorrhagic diathesis in Poland-China hogs was observed which clinically was similar to hemophilia.[25] However, it appeared to be inherited as a simple recessive characteristic, not sex-linked. During the last three years, in conjunction with Dr. Muhrer, we have compared porcine hemophilia with canine and human hemophilia.[26] Unlike classical hemophilia in dogs and humans, the prothrombin utilization test showed great variability in the bleeder swine. In some cases it was prolonged, whereas in other bleeder animals the prothrombin consumption rate was within the limits of normal animals. A comparison was then made of AHF levels of both normal and bleeder subjects in each of the three species. Both canine and human hemophilic substrates were used for the AHF assays. If the normal dog value is 100 per cent, then the normal human has roughly 20 per cent AHF, the swine 150 per cent. Neither the bleeder dog nor the human had any detectable AHF. The bleeder swine, however, had roughly 10 per cent as much of this clotting factor as is in normal dog plasma, or slightly more than 5 per cent of normal swine plasma. We concluded from this study that biochemically, regardless of their inheritance, these pigs were mild hemophiliacs, having only a trace of circulating AHF in their plasma. If the genetic studies on swine are correct, it indicates, in pigs at least, that the formation of

TABLE II—GRADES OF HEMOPHILIA

Patient	Grade	Age and Sex	Chief Symptoms	C.T. (min.)	P.T. (sec.)	P.T.T. (sec.)	Prothrombin Utilization (2-stage) or Consumption (1-stage) Tests	Plasma AHF (per cent)
1	Classical (severe)	28M	Hemarthroses, severe "internal" hemorrhage	>60	12	210	Impaired	0
2	Moderate	69M	Subcutaneous hematomas; post-operative hemorrhages	12	12	180	Normal	<3
3	Mild	18M	Post-operative hemorrhages	9	12	70	Normal	16
4	Subhemophilia	22M	Prolonged oozing, post-operative, one occasion	9	12	68	Normal	33
	Normal			9-11	12	65-75	—	70 or Above

C.T. = clotting time; P.T. = prothrombin time; P.T.T. = partial thromboplastin time.

this clotting factor is dependent upon another genic locus not on the X-chromosome, as it is in man and dog.

SOME ASPECTS OF DIAGNOSIS AND TREATMENT

Over the past several years it has become increasingly apparent that the diagnosis of hemophilia may be difficult. If the disease is mild, the usual clotting tests are negative; on the other hand, even if the disease is severe, it may be confused with a number of other hemorrhagic diatheses.

In our studies of hemophiliacs showing varying degrees of severity of the disease, we have used, in addition to the usual tests (clotting time, bleeding time, prothrombin time, two-stage prothrombin determination, prothrombin utilization test and platelet counts), two new procedures already mentioned, the partial thromboplastin time and a quantitative AHF assay. From these studies it appears that all gradations of hemophilia exist, from extremely severe to a state so mild that it defies detection by any test but an AHF assay. Depending upon the severity of the disease, hemophiliacs may be placed in one of four groups: 1) Classical or severe hemophilia; 2) intermediate or moderate hemophilia; 3) mild hemophilia; and 4) borderline hemophilia, or subhemophilia.[27] A patient

from each category is shown in Table II. Only the classical hemophiliac gave typical results with the usual diagnostic tests. The clotting time, the partial thromboplastin time and the prothrombin utilization test were all delayed and the prothrombin time was normal. In the moderate hemophiliac only a trace of AHF gave a normal clotting time and normal prothrombin utilization. The partial thromboplastin time, however, was prolonged. This test appears to provide a more sensitive indication of a clotting defect than does the prothrombin consumption test. With mild hemophilia, all tests are normal except for the AHF assay, which alone detected the clotting anomaly.

The subhemophiliac was of interest. A study was made of his four siblings. All had low AHF levels, 50 to 70 per cent of the usual control subject. This raised the question regarding the constancy of AHF levels in normal individuals. Repeated determinations of plasma AHF over a period of many months showed a remarkably constant level in a given individual. However, wide differences between normal individuals were observed. If the mean value of a group of normal subjects is taken as 100 per cent, most individuals are in the 80 to 120 per cent range; but over a two-fold spread was noted from the lowest (65 per cent) to the highest (136 per cent) values.[19] Advantage of this fact can be taken in selecting blood donors for hemophiliacs, using individuals at the upper end of the scale.

From these data and from a study of families, both hemophiliac and normal,[28] it appears that the level of plasma AHF is a function of the genic constitution of the individual. The gene determining the normal AHF level is dominant, designated by H. In classical hemophilia the gene is the recessive small *h*. Mild hemophilia appears to be determined by a series of alleles, one of the series being labeled h^m. For this reason we have called the milder types of hemophilia an allelic form of the disease. In normal individuals there also appears to be a series of alleles, or better isoalleles, which determines the normal AHF level. The gene related to the higher AHF level appears to be dominant. Although our studies on this point are not adequate to do more than make a tentative suggestion, it appears that by careful study of AHF in families, the inheritance of the dominant trait can be outlined.

An especially important problem in hemophilia is the identification of the female transmitters of the disease. In our study of heterozygotes, in canine hemophilia, porcine hemophilia and in mothers of classical

hemophilic patients, we have not been able to determine any difference from normal individuals in their blood coagulability. In one large family in which mild hemophilia occurred, determination of plasma AHF values was made in nearly all adult and adolescent members of the family.[28] By tracing the pattern of AHF levels from one generation to the next, the probable genic constitutions of certain individuals could be indicated. From this analysis, it was predicted that certain females would be heterozygous. All the women with male children actually were mothers of hemophiliacs. The genotype of the remaining women in the tentatively heterozygous category should be definitely determined before it will be known if the prediction value of this type of specialized study is sufficient to justify its use on a wider scale.

In summary, these studies on genetics in relation to AHF indicate that a steady state exists for this clotting factor in a given individual, and that the quantity of AHF in the plasma is probably determined by the genotype of the individual. Of a pair of alleles, the one related to the higher AHF level appears to be dominant. Thus the *quantitative* level of a specific plasma protein appears to be genetically determined, not a *qualitative* difference in a character, as is the usual case—for example, the qualitative differences in the genetically determined types of hemoglobin.

Another problem in the diagnosis of hemophilia is its separation from certain hemophilia-like states.[27] At least four separate diseases in this category have been recognized up to the present time. The nomenclature for these hemophilia-like diseases is both varied and confusing. We have arbitrarily called them hemophilioid diseases A, B, C and D (Table III). They resemble hemophilia in many ways. 1) All appear to be due to a plasma deficiency of a protein clotting factor necessary for the effective conversion of prothrombin to thrombin. 2) The hemorrhagic symptoms may be quite similar. 3) The diseases are congenital. 4) The clotting time and the partial thromboplastin time may be prolonged in all of them. In contrast to hemophilia, all have adequate amounts of AHF, except in the rare case of a combined disease. No agreement exists as to the exact function of these new clotting factors, except that, like AHF, they are needed if prothrombin utilization is to be prompt. In view of all of these things, we believe there is merit in using the relatively non-specific term *hemophilioid* for the group, until a better understanding of each clotting component is obtained.[29] If new diseases of this general

TABLE III—HEMOPHILIA AND THE HEMOPHILIOID STATES

Disease State	*Common Synonyms*	*P.T.*	*P.T.T.*	*P.T. Fortified**	*P.T.T. Fortified**
Hemophilia (Classical and moderate)	Hemophilia A	Normal	Prolonged	Normal	Normal
Hemophilioid State A	Parahemophilia, Ac Globulin, labile factor or proaccelerin deficiency	Prolonged	Prolonged	Normal	Normal
Hemophilioid State B	Spca, proconvertin, or stable factor deficiency	Prolonged	Prolonged	Prolonged	Prolonged
Hemophilioid State C	PTC deficiency, "Christmas Disease," Hemophilia B or II	Normal	Prolonged	Normal	Prolonged
Hemophilioid State D	PTA deficiency	Normal	Prolonged	Normal	Prolonged?

P.T. = prothrombin time; P.T.T. = partial thromboplastin time.

* Test plasma fortified by addition of equal vols. $BaSO_4$-treated normal plasma prior to performing tests.

type are recognized, they can readily be added to the list. In Table III, these diseases are arranged in chronological order, depending on the first clear description of the disease state, along with their common synonyms. Also shown in the Table is a relatively simple screening test that we have found useful for the presumptive diagnosis of hemophilia and the hemophilioid states. The clotting tests used are the prothrombin time (PT) and the partial thromboplastin time (PTT), with and without added normal plasma which has been treated with barium sulfate. The $BaSO_4$-treated plasma supplies a source of AHF and the A factor. Thus, in hemophilia the prolonged PTT becomes normal after fortification with the adsorped normal plasma. And similarly the prolonged PT and PTT in hemophilioid state A become normal with added adsorbed plasma. In hemophilioid state B, on the other hand, all tests remain prolonged, since the B factor is adsorbed by $BaSO_4$. Patients with the B pattern of tests may have hypoprothrombinemia, which can be excluded by using a modified two-stage test for prothrombin determination. The C and D hemophilioid states give the same pattern of results in this procedure. It should be pointed out that in mild hemo-

philia, and perhaps in mild forms of the hemophilioid states, the tests used in the screening procedure may reveal no abnormality.

A great many procedures have been advocated for the control of hemorrhage in hemophilia. Many agents have been tested under controlled conditions in our bleeder dogs, but only topical application of thrombin and transfusions of AHF-containing blood, plasma or plasma fractions have been effective. And AHF may not be effective in certain cases which have become refractory to transfusions.

In the treatment of bleeding from accessible sites, such as superficial wounds, epistaxis, or dental extraction sites, thrombin is the hemostatic agent of choice. Bovine thrombin should be used instead of human thrombin, since the latter is frequently contaminated with the hepatitis virus.[30] Prior to the application of thrombin, it is essential to remove the accumulated clots and expose the bleeding points. One of a number of vehicles may be used for thrombin, such as gelatin foam. Fibrin, freshly clotted out of a fibrinogen solution, or even out of citrated plasma, is a very satisfactory vehicle. Thrombin is added directly to the fibrinogen just before use. Most of the fluid is expressed from the clot, and immediately it is molded with pressure into the bleeding sites. It is best to maintain pressure, and to leave the thrombin-soaked fibrin or sponge in place, as removal disturbs the hemostatic clot, and bleeding recurs.

AHF may be administered as whole blood transfusions if the patient has a low hematocrit value. Otherwise, it is best to use whole plasma or a reconstituted lyophilized plasma. Plasma concentrates may be used, concentrating the plasma by Haurowitz' method of ice-separation on thawing or by other methods. The samples of Fraction I that we have tested have not had an AHF potency significantly greater than plasma, and many have been almost inactive. In the use of AHF, it is always well to reflect upon the utilization of this factor by the hemophiliac. The beneficial effect is of short duration, whether small or large transfusions are given. In other words, the hemophiliac appears to have no ability to store AHF. In the presence of continuing hemorrhage, with increasing stress on the hemostatic mechanism, larger amounts of AHF appear to be required than in the quiescent state. Hence larger and more frequent administration of AHF is required. We have suggested that the problem of treating a hemophiliac in a bleeding crisis is analogous to a problem in logistics. One needs to have the right thing in the right place at the right time. The right thing we believe is AHF. The right place is

everywhere in the vascular system; distribution of AHF is taken care of by the circulatory system. The right time is all the time, replacing as soon as possible the AHF which has been used up or lost. This last is the major problem in treatment of serious hemorrhage, if an adequate supply of AHF is at hand. The continuing supply of AHF can be accomplished by frequent plasma transfusions, every three to four hours if necessary, or better perhaps by continuous slow intravenous infusion.

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POLYCYTHEMIA VERA—ITS COURSE AND TREATMENT: RELATION TO MYELOID METAPLASIA AND LEUKEMIA*

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POLYCYTHEMIA vera or erythremia is a chronic progressive disease of insidious onset. It is characterized by an initial absolute increase in the number of erythrocytes which usually is accompanied by a leukocytosis, thrombocytosis, splenomegaly and ruddy cyanosis.

PATHOGENESIS

Theoretically, erythrocytosis may occur because of increased production of red cells, decreased erythrocyte destruction or a combination of both. The presence of polychromatophilic erythrocytes and occasionally normoblasts in the peripheral blood together with an erythroblastic hyperplasia in the bone marrow is strong evidence favoring increased erythrogenesis as the cause of the polycythemia. More definitive evidence for increased red cell production has been obtained by the use of radioactive iron[1,2] and isotopically labelled glycine.[3] Utilizing N_{15}, London et al. have shown that the erythrocytosis of polycythemia vera is due not to the production of red cells of increased longevity but rather to a two- to three-fold increase in the production of normal red cells and hemoglobin by the hyperplastic bone marrow.[3]

Since the original description of the syndrome by Vaquez[4] and its subsequent clinical delineation as a specific disease entity by Osler,[5] speculation has centered around the cause of the increased erythropoiesis. The early appreciation of the relation of the anoxemia of high altitude to erythrocytosis[6] and the polycythemia secondary to congenital heart disease and pulmonary conditions, has directed attention to bone marrow anoxia as the fundamental stimulus in erythremia. The production of this marrow anoxemia has encompassed many theories (Table I). An analysis

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TABLE I—SOME OF THE MOST COMMON THEORIES OF THE ETIOLOGY OF POLYCYTHEMIA VERA.

A. Increased red cell production
  I Anoxemia
    a) Anoxic
      Impaired pulmonary diffusion; vasoconstriction; increased tissue respiration
    b) Anemic
      Abnormal hemoglobin
    c) Stagnant
      Extreme capillary dilatation; sclerosis & fibrosis of marrow capillaries
    d) Competitive
      Myeloid hyperactivity
  II Humoral
    a) Excess intrinsic factor (Addisin); Hemopoietine
  III Hormonal

B. Decreased red cell destruction
    a) Increased life span of RBC

C. Neoplastic

of this multitude of theories relating to the etiology of erythremia and including anoxemia, hormones, humoral substances, neurogenic stimuli and others[7-10] is beyond the scope of this paper. Certain comments regarding the blood and bone marrow oxygen may be warranted, however.

No satisfactory evidence has been produced as yet substantiating any of these ingenious hypotheses leading to bone marrow anoxia. Rather, the bulk of the evidence suggests that anoxia per se is not the primary stimulus for the development of the erythrocytosis in erythremia. Definitive studies of the oxygen saturation of the bone marrow obtained by sternal aspiration by Schwartz and Stats,[11] and Berk and co-workers,[12] have shown either normal or increased oxygen saturation values in polycythemia vera. In the erythrocytosis secondary to anoxemia, leukocytosis, thrombocytosis and splenomegaly do not occur. The minimal oxygen unsaturation occasionally found in erythremia is probably of no significance in the production of the hypervolemia and the impaired pulmonary diffusion sometimes found in polycythemia vera[8] is rather an effect and not a cause of the erythrocytosis.

Because of its insidious onset and prolonged duration one is presented with a rare opportunity to study a disease throughout its complete course.[13] Only by an appreciation of the various developmental potentialities of erythremia can one intelligently theorize on the fundamental abnormality in this disease and its pathogenesis. Lawrence[14] and Wiseman and his co-workers[15] have emphasized the paucity of follow-up care in any large series of cases, studies on the whole being confined to only a small segment of the slowly developing syndrome. In the usual definition of the disease one is constantly reminded of the erythrocytosis that is invariably present, yet too few statements are made concerning the fact that this increased red cell mass may occur only during the initial phase of the disease and may even go undetected.

Within a few years following the original description of polycythemia vera, Türk[16] noted the frequent occurrence of granulocytic leukocytosis and the presence of immature red and white cells in the peripheral blood of patients with erythremia. He postulated an overactivity of the leukopoietic as well as the erythropoietic tissue, due to a primary hyperplasia of the marrow. The term erythremia was suggested to distinguish this disease from erythrocytosis secondary to anoxemia.

The concept of a total panmyelosis with expansion of the active red marrow to encompass the total potential marrow space received increasing support from biopsy and post-mortem examinations of the marrow in early erythremia; the frequent association of leukemoid and leukemic blood pictures, in some series running as high as 30 per cent,[14, 17] the occurrence of immature red and white cells in the peripheral blood and the thrombocytosis lend support to the hypothesis that erythremia is a chronic generalized bone marrow disease.

As cases of polycythemia vera were followed over a prolonged period of time, it was noted that the erythrocytosis was merely an initial facet of a complex disease process. This disease frequently terminated in leukemia, osteosclerosis, myelofibrosis, myeloid metaplasia and other diverse pathological entities. The concept of the neoplastic nature of erythremia thus arose and the disease now is becoming recognized as having a similar origin as other myeloproliferative syndromes.[18-21] Against the neoplastic nature of erythremia has been the relatively prolonged course of the disease and the apparent lack of invasiveness manifested by the proliferating cells. However, well differentiated malignant cells are functionally close to normal cells and may have a benign course for

many years.[22] Wiseman[23] has noted that "in a blood cell strain, it is only the cell in the end-stage of maturation that regularly shows appreciable and visible quantitative increase under conditions of stimulation, not the precursor cell."

An appreciation of the protean pathological findings seen in polycythemia vera of long duration has crystallized an evolutionary pattern that encompasses all the variations seen. It has long been obvious that stimulation of a particular hematic cell series in the marrow often induces a reactive response in the other hematic cellular components, e.g., following hemorrhage, not only is there a hyperplasia of the red cell series but of the white cells and platelets as well. Erythroleukemia shows proliferation of both the erythroid and myeloid marrow precursors, and stimulation of the megakaryocytes with extreme thrombocytosis is not infrequent in myeloid leukemia.

It appears that the marrow cells may proliferate as an hematic unit,[19] the clinical and pathological picture depending upon the degree of the stimulus transmitted along any specific cellular line. This concept of total marrow hyperplasia in response to a stimulus implies an antecedent proliferative stimulus exerted on the precursor cell or cells of the differentiated hematic cells. One may therefore consider an initial growth stimulus directed at the primitive mesenchymal or reticulum cell from which all embryonal and adult blood cells as well as fibroblasts and osteoblasts are formed and then, in varying degrees, specific stimuli directed toward special cellular compartments (Fig. 1).

In the embryo blood cell formation occurs not only in the bone marrow but in extra-osseous organs as the liver and spleen. Localization of hemopoiesis to the marrow cavity shortly before birth results in a physiologic regression of these heteroplastic foci derived from the cytoplasmic reticulum. Nonetheless, these sites retain their potential functional capacity to produce differentiated hematic cells when stimulated.[21,24] Klemperer[21] has noted that "stimulation of the undifferentiated mesenchyme may lead to local or generalized proliferation" with specific cellular differentiation generally occurring. The common denominator of the adult functioning bone marrow and the potential extra-osseous marrow in the liver and spleen is the undifferentiated mesenchyme or cytoplasmic and fibrillar reticulum.[21] Presumably then, a stimulus directed at the reticulum in the marrow will simultaneously produce a like response in the dormant extra-osseous mesenchymal cell. The resultant

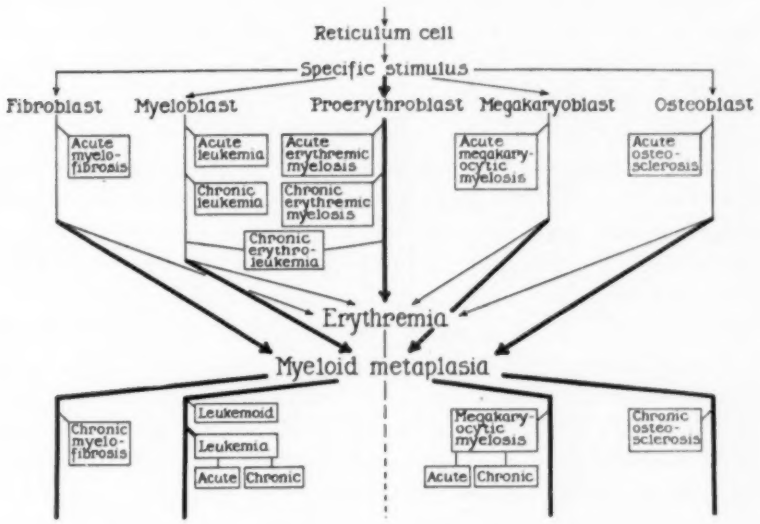

Figure 1: Schematic concept of the interrelationship of polycythemia vera (erythremia) with myeloid metaplasia and other proliferative diseases of the reticulum. Stimulation of the primitive reticulum cell must be hypothecated to account for the proliferation of all hematic and non-hematic mesenchymal derivatives occurring in polycythemia vera. Qualitative and quantitative variations in the intensity of the stimuli will determine the hematologic and pathologic changes occurring during the course of erythremia, e.g., megakaryoblast stimulation to produce thrombocytosis or megakaryocytic myelosis and stimulation of the white cell precursor to produce a leukemoid or leukemic picture. Fibroblastic and osteoblastic hyperactivity may result in myelofibrosis or osteosclerosis ("spent polycythemia"). Erythremia and myeloid metaplasia are closely related, the latter probably always associated with erythremia of sufficient duration. With development of extramedullary hematopoiesis, erythrogenesis may diminish as denoted by the dotted line whereas other specific stimuli appear to grow more intense (heavy lines). Myeloid metaplasia may occur without antecedent erythremia, the erythrogenetic stimulus initially appearing normal or diminished, whereas the other stimuli are increased from the onset (note heavy lines bypassing erythremia). The hematologic and pathologic picture in myeloid metaplasia associated with polycythemia vera of long duration and that of the idiopathic variety are indistinguishable. (Modified from Rosenthal, M. C.,[24] *Bull. New England Med. Center 12:*154, 1950.)

pathological picture will depend on the locus of the stimulated cells and the qualitative and quantitative nature of the stimulus, whether along hematic, fibroblastic or other lines of development and whether it be an acute or chronic disorder. In polycythemia vera the initial fundamental disturbance may very well be a reticulosis and the extramedullary blood formation which always accompanies polycythemia vera of a sufficiently long duration is probably of autochthonous origin and is not compensatory.[24]

A concept such as this offers an attractive hypothesis for the numerous transitional clinical and pathological findings frequently encountered in polycythemia vera, leukemia, myelofibrosis, osteosclerosis and associated syndromes. The quantitative variation in simultaneous stimuli occurring over a period of months or years will produce disease forms that have as the only abnormality common to all, pathological cell proliferation. This concept is graphically illustrated in Fig. 1. A hypothetical growth stimulus acting on the undifferentiated mesenchymal cells may produce one or more specific stimuli acting simultaneously but quantitatively different. Thus, the acute syndromes are usually manifested along one potential line of development, show invasive, disorganized, neoplastic tendencies of the proliferating cells and are rapidly fatal. Even in the acute syndromes the appearance of two or more simultaneously stimulated cellular categories may occur. In the few cases of acute erythremic myelosis studied by us, although initially the bone marrow and peripheral blood were predominantly erythro-normo-blastic, these patients always died with the characteristic blood and marrow findings of acute myeloblastic leukemia. It would appear that the erythrogenetic stimulus eventually spent itself or was transformed and a myeloblastic one prevailed terminally. In chronic leukemia the stimulus may not be as intense and may be accompanied by erythroid hyperactivity resulting in a picture of erythroleukemia; a more pronounced erythrogenetic stimulus might produce a picture of chronic erythremic myelosis (Fig. 1). Simplification of this chart to include only the more important syndromes should not eliminate the fact that other lines of development may simultaneously undergo increased proliferative activity.

In the case of erythremia the stimulus to erythropoiesis initially predominates, although simultaneous stimulation of the granulocytic and platelet precursor cells produces the leukocytosis and thrombocytosis usually a part of polycythemia vera. Non-hematic increased cellular activity in the fibroblasts and osteoblasts also occurs with fibroblastic and osteoblastic as well as reticulum cell proliferation, the latter being more obvious in the spleen. The initial stimulus must also be qualitatively different in this disease, since the development of all cells is along rather orderly lines. The bone marrow and peripheral blood reflect the generalized hyperactivity with panmyelosis of the marrow (Fig. 2), and immature red and white cells and increased platelets in the peripheral blood.

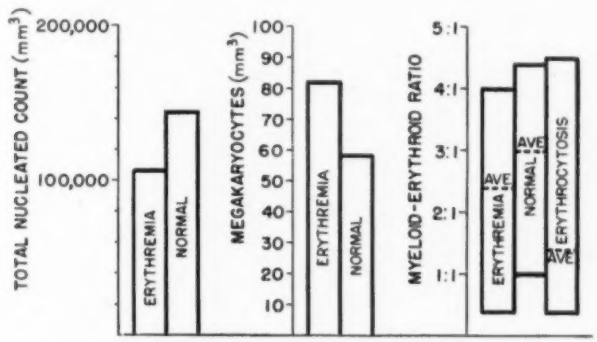

Figure 2: Average bone marrow results in normal patients and 131 cases of polycythemia vera before treatment contrasted with erythrocytosis (secondary polycythemia). The questionable reduction in total nucleated count and the slight increased megakaryocyte concentration in the bone marrow of erythremia are accompanied by a decreased M:E ratio (ave. 2.5:1 range 0.5-4:1). Because of extreme overlapping in all groups however marrow aspiration findings are rarely helpful as a diagnostic aid.

The extra-osseous potential marrow space appears to undergo the same proliferative activity and the liver and spleen become enlarged due to hyperplasia of the cytoplasmic and fibrillar reticulum. The occurrence of myeloid metaplasia during a period of hyperplasia in the bone marrow seems to negate the concept of compensatory heteroplastic blood formation. Accordingly, erythremia and myeloid metaplasia go hand in hand. Our cases of erythremia of long duration have invariably shown some degree of myeloid metaplasia in the liver and spleen with varying fibrosis in the marrow at autopsy. With sufficient passage of time, changes begin to appear in erythrogenesis. Red cell formation begins to falter and other lines of development appear to gain ascendency. Thus the phase of polycythemia vera with so-called polynuclear cell leukemia or the syndrome of myelofibrosis may appear. In other cases the megakaryocytes predominate with the resultant picture of acute or chronic megakaryocytic myelosis; still others display hyperactivity of the osteoblasts and bone formation encroaches upon or completely replaces the marrow activity, analogous to the fibrous tissue of myelofibrosis. At this phase of the disease one may see a severe anemia, a leukemoid or leukemic blood picture, thrombocythemia or thrombopenia all in a patient who a number of years before had a severe polycythemia.

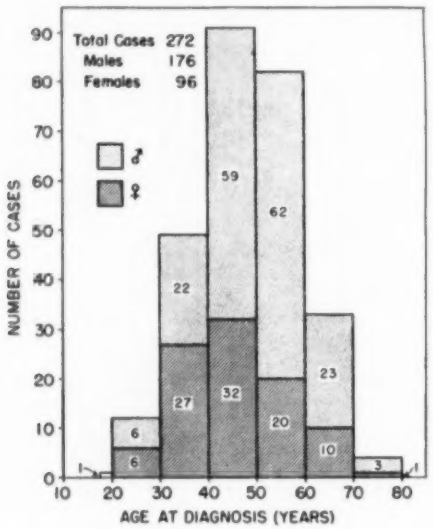

Figure 3: Age and sex distribution in 272 cases of polycythemia vera. The average age at the time of diagnosis was 48.1 years with a male to female ratio of 1.8:1.

This dynamic concept brings together the multitude of variegated names and syndromes representing one common disease entity, erythremia.

Myeloid metaplasia and myelofibrosis need not necessarily be associated with polycythemia vera but may be idiopathic in type. Of sixty-one cases of myelofibrosis with myeloid metaplasia studied by us,[25] eight (13 per cent) instances occurred in known polycythemics who had been followed in our clinic, fifteen (25 per cent) had histories and laboratory findings before admission to the hospital typical of erythremia, and twelve (20 per cent) had histories suggestive of polycythemia vera but no correlative laboratory data. Thus thirty-five or 58 per cent of sixty-one cases of myeloid metaplasia with myelofibrotic marrows had a probable antecedent polycythemic phase and 42 per cent were apparently idiopathic. Presumably, in the idiopathic variety not preceded by erythremia, erythrogenetic activity remains normal or is suppressed at a very early phase of the disease while hyperactivity of the other hematic and fibroblastic components occurs. With this above pathogenetic concept

TABLE II—LABORATORY AND CLINICAL FINDINGS IN POLYCYTHEMIA VERA

A. LABORATORY
1. Erythrocytosis
2. Granulocytic leukocytosis
3. Thrombocytosis
4. RBC & WBC immaturity
5. Panmyelosis
6. Red cell volume increased
*7. Oxygen saturation normal
8. Plasma iron turnover increased
9. Red cell iron turnover increased
10. Blood pigments normal

B. CLINICAL
1. Symptoms
   a) Cardiovascular
   b) Neurologic
   c) Gastrointestinal
   d) Hemorrhagic
2. Plethora
3. Hepatomegaly
4. Splenomegaly
5. Cardiac normal; pulmonary normal

*The arterial oxygen saturation is the only test capable of differentiating between polycythemia vera and erythrocytosis secondary to anoxemia.

of polycythemia vera and myeloid metaplasia the clinical course of the disease may be more comprehensible.

COURSE

Polycythemia vera is primarily a disease of middle age with an average age at diagnosis in our group of cases of 48.1 years and ranging from eighteen to seventy-nine years. The distribution of cases in males to females is 1.8:1 a ratio in accord with other reports[14,17,26] (Fig. 3).

The course of polycythemia vera is one of many years' duration in the satisfactorily treated case. A normal life expectancy for persons in this age group is about sixty-eight years,[14] and in those cases of erythremia carefully followed and successfully treated, this life expectancy may be attained and exceeds that for pernicious anemia or diabetes.[27]

There is an asymptomatic developmental phase, the duration of which must remain conjectural although Dameshek has ascribed a period of about five years for this.[28]

Subsequently, during the stage of erythrocytosis lasting from five to twenty years with its myriad of symptoms referable primarily to the hypervolemia and pancytosis, the diagnosis is usually made (Table II). Many patients may remain asymptomatic during this period[29] despite the abnormal pancytosis and the diagnosis may be made only during a fortuitous routine examination.

Polycythemia vera does not signify only a hypervolemic phase however. The disease progresses inexorably through its cycle, producing one picture at one time and another hematic response may prevail at another. A period of relative normalcy as far as the red cells are concerned may follow the polycythemic stage producing the so-called remissions that have been reported.[28,29] This phase should be looked upon as the first sign of diminished erythropoietic activity in the marrow and the early development of the syndrome of myeloid metaplasia. Careful examination of the blood and marrow at this time will show a relatively normal red cell concentration with a leukocytosis and thrombocytosis. The blood smear shows a leukoerythroblastic blood picture with a few myelocytes and normoblasts.[19,20,30] The red cells, particularly, are characteristic of the developing metaplastic blood formation, there being polychromatophilia and marked aniso- and poikilo-cytosis with microcytes, elliptical cells, "teardrop" cells and other bizarre red cell forms. These red cell changes are characteristic of either this stage of polycythemia vera or of the idiopathic type of myeloid metaplasia. It is not unusual to have a marked granulocytic leukocytosis at this time with a thrombocytosis of one or two million featuring abnormally large platelets or even megakaryocytic fragments in the blood. The so-called polynuclear cell leukemia probably falls into this group of early myeloid metaplasia. The marrow still may be hyperplastic but instead of showing a panmyelosis it now shows some reduction in the erythropoietic elements with an increase in the myeloid cells, the fibrillar and cytoplasmic reticulum and megakaryocytes. The erythroid foci appear to be reduced due to the encroachment by other hyperactive cellular components. Whether this is due to degeneration of the red cell precursors with replacement by other cellular systems or is due to increased stimulation and hyperactivity of the white cells, fibroblasts and megakaryocytes is not known. Simul-

taneously with the marrow changes, the spleen enlarges and becomes the site of extramedullary blood formation. A splenic puncture done at this time or subsequently will show a picture similar to that seen in the marrow with reticulum cell hyperplasia and hematic cell proliferation, the findings of myeloid metaplasia[31] (Fig. 4).

The changes in the marrow and spleen proceed unchecked with marrow proliferation of fibroblasts and increasing encroachment upon the erythroid tissue. It must be remembered that although hematic cell activity diminishes in varying degree, the marrow still remains the site of extreme proliferative activity. Fibrosis and osteosclerosis merely signify that the stimuli, spent as far as the red cells are concerned, now show increasing activity toward the other hematic cells as well as toward the non-hematic mesenchymal derivatives, the fibroblasts and osteoblasts. The early spent phase is thus merely a later stage in the naturally determined course of the disease. The red cell activity may be gradually relocated to extramedullary sites (Fig. 4) and because of the abnormal forms produced, anemia may become prominent. These red cells from extra-osseous sites have been shown to have a shortened survival[32] but if extra-osseous formation is great enough, anemia may be mild or even absent and a compensated myelofibrotic state may be seen that may last for months or years. The marrow eventually becomes almost completely fibrotic with megakaryocytes now prominent due to disappearance of most of the other cellular elements; reticulum cells, osteoblasts and a few white cells may remain. At this stage one encounters a "dry tap" on marrow aspiration and the peripheral blood shows anemia, leukopenia and a variable platelet count although thrombocytopenia is usual (Fig. 4). Other developmental possibilities remain in that with the progression of the disease white cell hyperactivity may predominate resulting in a terminal picture of myeloid leukemia. In some cases the degree of megakaryocytic hyperactivity may be such that the condition has been called megakaryocytic leukemia or myelosis; in others, megakaryocytic, myelocytic, fibroblastic and osteoblastic activity may all be stimulated to produce complex clinical and post-morten findings.

Complications and Treatment

The treatment of chronic diseases of unknown etiology should be directed toward symptomatic relief as well as correction of the altered physiologic state for as long a period of time as possible. It follows that

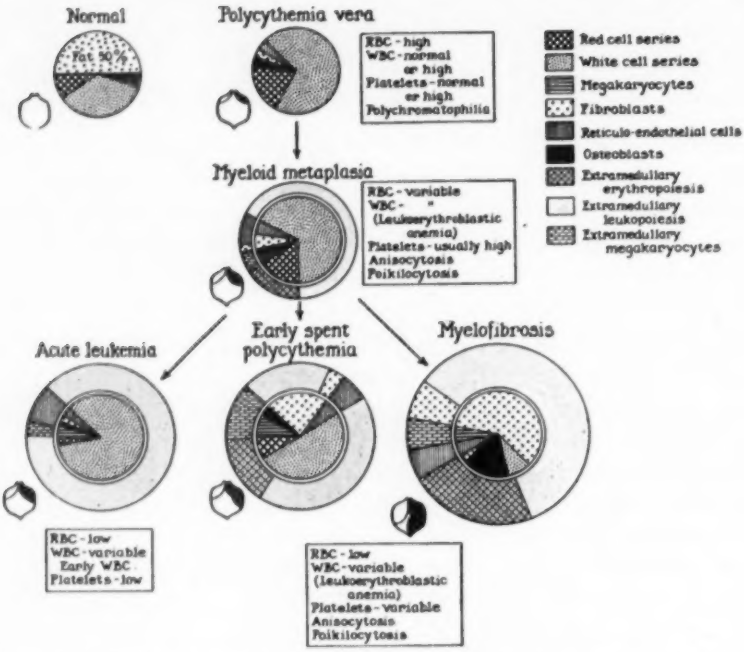

Figure 4: Hypothetical concept of the course of polycythemia vera. The blood, bone marrow and extra-osseous potential marrow, considered "the blood tissue," reflect simultaneous changes occurring during the course of polycythemia vera. In polycythemia vera the hyperplastic marrow expands to encompass the total marrow space at the expense of the fat cells. There is a panmyelosis with stimulation of all hematic and non-hematic cellular derivatives of the reticulum cell. Blood examination reveals an erythrocytosis and usually a granulocytic leukocytosis, thrombocytosis and immature red and white cells. Splenomegaly and hepatomegaly are frequently present, initially due to the increase in blood volume but subsequently associated with reticulum cell hyperplasia and heteroplastic blood formation. With continued hyperactivity the dormant extra-osseous potential marrow becomes functionally active and the site of extramedullary hematopoiesis (stage of myeloid metaplasia) as the spleen and liver enlarge (outer circle designates extramedullary blood formation). The bone marrow shows diminution in erythrogenesis and proliferation of reticulum cells, fibroblasts, megakaryocytes and white cells. The peripheral blood mirrors the marrow changes with usually a mild to moderate anemia although normal values (compensated state) may prevail for many years. Thrombocytosis is common as is a leuko-erythroblastic blood picture. With time, progressive changes in cellular composition of the marrow occur (stage of early spent polycythemia). Fibroblastic or osteoblastic proliferation encroaches on hematic cell activity with a reduction particularly in erythropoiesis. Megakaryocytes appear more plentiful due either to increased proliferative activity or a quantitative decrease in other hematic cells. The liver and spleen, the site of extramedullary hematopoiesis, are not encased in bone, hence can expand markedly. There is now a leukocytosis and thrombocytopenia or thrombocytosis, leuko-erythroblastic anemia with morphologically bizarre red cells. Further fibroblastic or osteoblastic proliferation may obliterate the marrow cavity with all blood formation occurring in the extra-osseous marrow (stage of myelofibrosis). Note that nonhematic cell proliferation occurs in the liver and spleen also. The anemia becomes more severe with usually a leukopenia, thrombopenia and a more marked leuko-erythroblastic blood picture. Hepatosplenomegaly may be tremendous. This phase of myelofibrosis (myeloid metaplasia) may be a terminal picture in polycythemia vera. Other lines of proliferation may gain ascendency, e.g., the white cells, with development of an acute leukemia occasionally preceded by a stage similar to chronic myelocytic leukemia; megakaryocyte hyperactivity may result in so-called megakaryocytic myelosis, etc.

Acute leukemia, spent polycythemia and myelofibrosis are all depicted as stemming from a common stage of myeloid metaplasia. Variation in proliferative activity of any combination of cellular categories may produce complex clinical and pathological syndromes. Thus, well developed myelofibrosis may frequently show large numbers of myeloblasts and myelocytes in the blood and, similarly, a terminal acute blastic leukemia may show extensive fibroblastic proliferation. (The area represented for any specific cellular series is only approximate and merely represents an attempt to demonstrate graphically a few of the multiple developmental potentialities in polycythemia vera.)

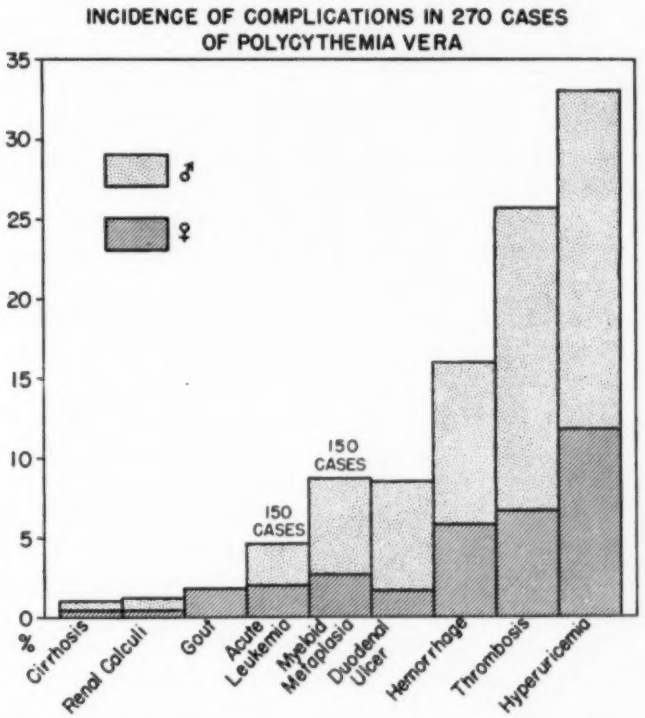

Figure 5: Incidence of complications in 270 cases of polycythemia vera. The data of only 150 cases could be utilized for determining the per cent incidence of acute leukemia and myeloid metaplasia. These latter should not be classified as complications since they are stages in the course of polycythemia vera.

comfort to the patient, ease of administration of the therapy, reduction in complications and morbidity and return to a normal social and economic status for the patient should be achieved if possible with the therapeutic method employed.[14, 15, 17, 27]

The symptoms and complications of erythremia are directly related to the increased blood volume and viscosity, and the panmyelosis (Fig. 5). Sufficient data have been reported on the incidence and type of complications occurring in erythremia prior to the use of myelosuppressive agents.[14, 17, 27, 28, 33-35] Thus Stroebel et al.[17] report an incidence of 31.1 per cent hemorrhage and thrombosis, 27 per cent hyperuricemia and 32

per cent leukemoid reactions in erythremia prior to internal radiation therapy. Analysis of the cause of death in this group as well as in others[14, 26] again emphasizes the increased proportion of vascular accidents, 56 per cent of the patients dying of hemorrhage or thrombosis; in our series of patients the direct relation of complications to the hypervolemia and panmyelosis is also apparent (Fig. 5, Fig. 7).

Elevation of the serum uric acid to over 5 mg. per cent in females and 6 mg. per cent in males occurred in 32 (12 per cent) and 57 (21 per cent) respectively, values similar to those reported.[17] Despite the hyperuricemia found in 33 per cent of the cases, gout was a rare complication, occurring or developing in only five (1.9 per cent) of our patients and only two (0.8 per cent) cases of renal calculi were seen. The incidence of gout in erythremia has been reported as somewhat higher varying from 4.7 per cent to 10 per cent[26, 36] with probably a greater number of cases occurring in the spent phase of the disease.[25, 37] One might expect a greater incidence in view of the tremendous cellular catabolic activity with degradation of nucleoprotein to purines and uric acid. The relationship of serum uric acid to the level of red and white blood cells is illustrated in Fig. 6. No particular correlation appears evident, some of the highest red and white cell concentrations showing normal uric acid levels whereas the reverse situation frequently prevailed. Following myelosuppressive therapy as contrasted with the conventional therapy of venesection and hemolytic agents, the serum uric acid, when elevated, invariably returned to normal levels. The fact that high uric acid levels occur with normal red and white blood cell concentrations, and diminish following marrow suppressive therapy, seems to indicate increased proliferation of hematic and non-hematic cells in the marrow with a probable failure of delivery or death of many of the cells produced.

During the course of the disease vascular accidents occurred in 42 per cent of the group, with thrombosis or phlebitis accounting for 26 per cent and hemorrhage 16 per cent (Fig. 5). The latter figure does not include minor hemorrhagic manifestations such as bleeding from the gums or nose, easy bruisability or occasional petechiae but rather hemorrhages severe enough to require medical attention. This high incidence of vascular accidents may be contrasted with results in a group of 128 of our cases treated with radioactive phosphorus or triethylene melamine. In this group, thirty-one instances (24 per cent) of thrombosis and

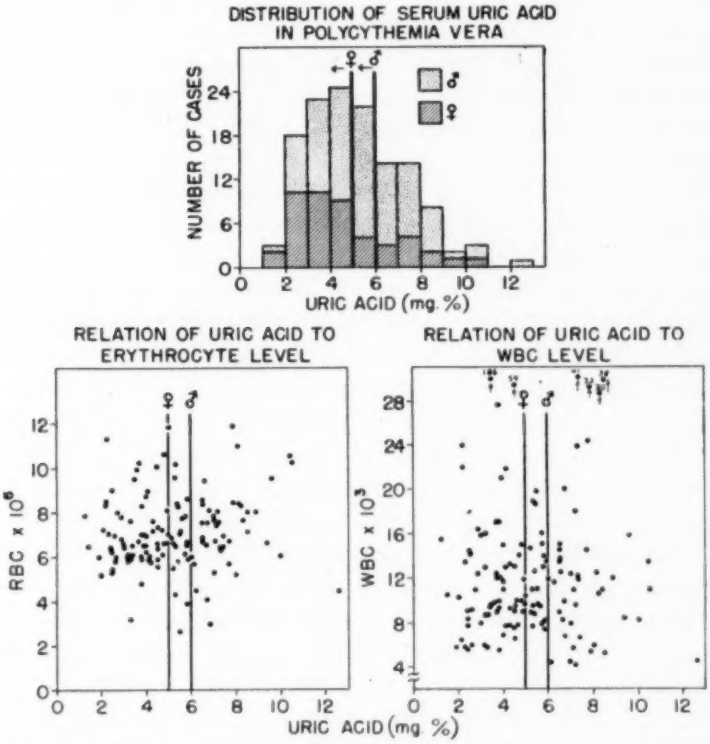

Figure 6: Uric acid levels in polycythemia vera. Note the lack of correlation between hyperuricemia and elevated red and white cell levels.

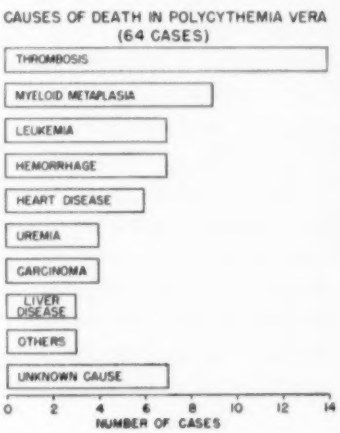

Figure 7: Causes of death in 64 cases of polycythemia vera treated by all forms of therapy. "Leukemia" refers only to the acute type; myeloid metaplasia includes myelofibrosis and all associated pathological entities. Where hemorrhage, thrombosis, etc. occurred as a direct cause of death in advanced myeloid metaplasia, death was classified as being due to myeloid metaplasia only.

twelve (10 per cent) of hemorrhage occurred prior to therapy whereas only seven patients (5.5 per cent) developed thrombotic manifestations and three (2 per cent) showed a hemorrhagic tendency after the use of myelosuppressive agents. Of the seven cases developing thrombosis after treatment, five occurred either in cases difficult to control or inadequately treated.

Peptic ulcer has been reported as occurring in 7 per cent to 20 per cent of patients with polycythemia vera.[14, 26, 29] In our group, 8.6 per cent had definite roentgenologic evidence of gastric or duodenal ulceration although about 50 per cent of the patients complained of gastrointestinal disturbances. Thrombosis of small mesenteric vessels as well as impaired circulation due to the capillary dilatation probably account for the increased incidence of ulcer in erythremia.

Leukemia and myelofibrosis with myeloid metaplasia should not truly be classified as complications but rather as stages of erythremia occurring incident to the natural course and duration of the disease. All patients with polycythemia vera will develop anemia and qualitative and quantitative changes in the white cells and platelets with marrow fibrosis and extramedullary hemopoiesis if they do not succumb to one of the complications noted previously. Chronic myelocytic leukemia was definitely seen in only one patient who finally died of acute myeloblastic leukemia (Fig. 14). The designation of leukemoid and chronic leukemic pictures in erythremia are confusing, the former merely reflecting the myeloid hyperactivity and the latter, heteroplastic blood formation with excessive stimulation of the myeloid cells. Full blown myeloid metaplasia was found in thirteen cases or 8.6 per cent of 150 cases with at least a five year history and seven additional patients (4.7 per cent) developed acute leukemia terminally.

Further analysis of the causes of death in polycythemia vera again demonstrates the dangers of the pancytosis (Fig. 7). Of sixty-four deaths in our group of polycythemia vera cases, vascular accidents accounted for twenty-one or about 33 per cent, thrombosis occurring in fourteen (22 per cent) and hemorrhage in seven (11 per cent). This latter group does not include those dying of hemorrhage in the terminal phases of the disease but rather represents cases of early erythremia without myeloid metaplasia or leukemia.

The next most frequent cause of death occurring in nine patients (14 per cent) was so-called "spent polycythemia" or myeloid meta-

plasia with myelofibrosis. Hemorrhage, infection or cardiac failure is usually present and precipitates the terminal event.

The incidence of carcinoma in this disease, about 6 per cent, does not appear to be any greater than in the general population. Four patients (6 per cent) died of uremia secondary to nephrosclerosis and not associated with renal calculi and hyperuricemia as may occur in the lymphomatous diseases. It is interesting that in the group classified as "others," one patient had extensive tuberculosis with splenic involvement, one multiple myeloma and the third Hodgkin's disease. The occasional association of the latter two diseases has been noted before and lends support to the unitarian concept of the reticuloses.[14, 23] Eight additional patients were known to have died but the direct cause of death could not be ascertained.

The occurrence of leukemia in erythremia as an end result of the natural course of the disease or as a complication of radiation therapy has been the subject of many reports.[13, 14, 22, 26, 27, 35, 38-40] Unfortunately, comparable statistics for large series of cases treated in various ways are not available and careful follow-up studies were practically non-existent prior to the use of internal radiation therapy as supplied by radioactive phosphorus. Seven patients (11 per cent of sixty-four deaths) died with acute myeloblastic leukemia. Treatment in three cases consisted of radioactive phosphorus and phlebotomy, one patient receiving a total of only three millicuries P^{32} two and a half years prior to death. One patient received one course of x-ray to the spleen three years prior to his exitus, treatment otherwise consisting only of venesections. Three cases were treated with venesections, local x-radiation to the long bones or spleen and multiple courses of radioactive phosphorus when it became available. In general, those cases terminating in an acute leukemia were most difficult to control,[17] the erythrocytosis usually being accompanied by a prolonged leukemoid blood picture and marked splenomegaly.

Incidences of leukemia, ranging from 10 to 30 per cent or more, have been noted in erythremia, the majority of cases being of the chronic myelocytic type with only an occasional case of acute leukemia appearing.[14, 27, 39] In the light of present experience wherein seven out of sixty-four or 11 per cent of deaths in our cases of erythremia, 14 per cent as reported by Lawrence,[14, 27] 30 per cent in Wiseman's[15] collected series and 18 per cent in the Mayo group reported by Stroebel[17] were due to acute myeloblastic leukemia, and chronic myelocytic leukemia was seen

as a terminal picture in only four cases of the above combined series, some factor or factors must be implicated.

Twenty-five per cent of the deaths in our series were due to both myeloid metaplasia with myelofibrosis and acute leukemia; 27 per cent of the deaths in Stroebel's group terminally showed acute leukemia, chronic myelocytic leukemia or aplastic anemia and 20 per cent in the series reported by Lawrence were of the same categories. Thus of 144 deaths (sum of above three series) in polycythemia vera treated with x-ray or P^{32}, about 25 per cent were due to leukemia and myelofibrosis. This may be contrasted with the higher combined mortality statistics for acute and chronic leukemia, "aplastic anemia," myelofibrosis and myeloid metaplasia following treatment with venesection, phenylhydrazine or radiation. That acute leukemia can occur as a terminal event in erythremia treated only by venesection was demonstrated recently in two cases followed by Dameshek.[41] Tinney and his associates[42] reported the high incidence of leukemia, as much as 80 per cent, occurring in patients surviving over fifteen years, and emphasized the direct relation between duration of the erythremic state and abnormal white cell proliferation.

The life span of polycythemia vera patients treated with P^{32} as reported by Lawrence[14] far exceeds that of other groups not so treated. A median survival of 13.2 years for polycythemia vera treated with radiophosphorus was found in his group as compared with about 6.7 years noted by Videback.[26] It seems reasonable to conclude that through the use of marrow suppressive therapy, the duration of the disease is prolonged and patients who would probably have died at one of the earlier phases of the disease are now being carried to the end stages of erythremia until complete disorganization of hematic cell proliferation occurs.

Reduction in the blood volume, suppression of the increased marrow activity and reduction in the white cells and the platelets are all a necessary feature of any successful treatment of polycythemia vera. The danger of severe hemorrhage or thrombosis always exists and sound therapy should be directed toward rapid amelioration of not only the symptoms but, more important, normalization of the sluggish thrombocythemic blood by means of a marrow suppressing agent. It is not unusual to see coronary thrombosis, cerebral thrombosis or hemorrhage, pulmonary infarction and gastrointestinal hemorrhage occur while

therapy is being contemplated or during the process of adhering to a minimal treatment policy.

At least brief mention should be made of the problem of coagulation and hemorrhage in polycythemia vera. It is paradoxical that despite normal or elevated blood platelets, bleeding at times may be extensive. Death due to exsanguination has occurred in erythremia particularly following surgery.

Patients with erythremia with elevated packed cell volumes and thrombocytosis seem to have poor clot retraction.[43] Clot retraction may actually occur rapidly, but because of the increased red cell volume, only a few red cells are caught in the fibrin mesh, and a tiny but well retracted clot is formed leaving most of the red cells free in the serum thus giving the appearance of poor clot retraction.[44] The bleeding and thrombotic tendency are directly correlated with increased viscosity and red cell mass and thrombocytosis. Again the need for a total myelosuppressive agent in the treatment of this disease is indicated. Further studies in our laboratory by M. C. Rosenthal[45] have indicated all plasma and cellular components now tested for in a bleeding diathesis to be within normal limits. The possibility that reduced plasma concentration results in a relative deficiency of fibrinogen or some other clotting factor could not be substantiated. Similarly the infusion of large amounts of fibrinogen solution intravenously was not successful in stopping or preventing continued hemorrhage in polycythemia vera.

Elective major or minor surgical intervention should not be contemplated unless normalization of the cellular components has occurred. Despite reduction in blood volume these patients may show serious postoperative bleeding[28] directly related to their unusual and complex hemostatic defect. In our group of patients four deaths attributable to exsanguination occurred following surgery despite the reduction in blood volume by hemorrhage and the use of fresh blood, plasma, fibrinogen and local agents.

Necessary elective surgery may be attempted in patients with polycythemia vera after the blood values have been normal for a few months. For those surgical emergencies where slow reduction in blood cells is not possible, venesections plus careful hemostasis should be utilized. Hemorrhage, however, remains an ever threatening problem as does postoperative thrombosis. Again the use of P^{32} or TEM has reduced these complications. Early ambulation and other preventative measures

TABLE III—ANALYSIS OF AGENTS USED IN THE TREATMENT OF ERYTHREMIA

1. P^{32}
   a) Treatment of choice at this time
   b) Effective in over 75% of cases
   c) Dosage must be individualized
   d) Easily administered, no reactions

2. TEM
   a) Nausea & vomiting in 1/3 of cases
   b) Marked variability in response
   c) Minimal effective dose through trial and error
   d) Remissions short-lived
   e) Safety factor small
   f) Results as with P^{32}

3. SPRAY IRRADIATION
   a) Results as with P32
   b) Radiation sickness

4. PHLEBOTOMY
   a) Effect usually rapid but temporary
   b) Iron deficiency produced
   c) Marrow stimulated
   d) Platelets and WBC increase
   e) Circulatory collapse may occur

5. PHENYLHYDRAZINE
   a) Dosage uncertain and variable
   b) Platelets and WBC increase
   c) Marrow stimulated

6. NITROGEN MUSTARD
   a) Variability in response
   b) Remissions short-lived
   c) Severe reactions

7. FOWLER'S SOLUTION
   a) G-I symptoms
   b) Effect variable

TABLE IV—PRINCIPLES OF MANAGEMENT OF POLYCYTHEMIA VERA

1. Rapid reduction of blood volume to normal levels:
   (R: 300-500cc phlebotomy q 2 days)

2. Suppression of increased marrow activity:
   (R: P32 intravenously or TEM orally)

3. Maintenance of cellular elements at normal level:
   (R: CBC q 4-6 weeks)

4. Avoid overtreatment
   R: P^{32}—no more than 5-7 mc I.V. in 6 months
   R: TEM—start with 10 mg. in first course. Do not repeat for 2 months
   R: Phlebotomy in resistant cases

5. Elective surgery contra-indicated unless control established

should be instituted as soon as possible. Anticoagulants are not well tolerated and extensive hemorrhages have occurred following their use; thus heparin, Dicumarol and similar prothrombin reducing agents should be avoided. If anticoagulant therapy is imperative, heparin is the agent of choice.

Until recently the treatment of erythremia had presented a difficult problem. Attempts to bring about a normal physiological state had been directed toward either removal of the excess quantities of blood or the use of a hemolytic agent such as phenylhydrazine[22, 26, 28] (Table III). Neither of these methods was particularly satisfactory since control was difficult and their use indirectly stimulated erythrogenesis. Removal of blood over a prolonged period of time invariably results in an iron deficiency state with production of hypochromic microcytic polycythemia. Although erythropoiesis may be impaired, the other cellular components appear to be stimulated. The serum iron in these cases is exceedingly low and reflects the number of venesections performed. Signs and symptoms of severe iron deficiency such as glossitis, sore mouth and dysphagia have been produced, which respond only to iron therapy. Although the major part of the body iron is in the hemoglobin molecule nevertheless iron is an essential trace element for most metabolic activities and its drastic reduction may seriously impair normal cellular function. When severe iron deficiency is present we have attempted to correct it in conjunction with our usual forms of therapy.

Spray irradiation or deep x-ray therapy to the long bones has been used with success in the treatment of erythremia.[14, 28, 46, 47] As with P^{32} or TEM, because of the relatively slow action of roentgen therapy, prior venesection should be utilized to produce rapid normalization of the blood volume. Frequently, however, radiation sickness may be most uncomfortable to the patient. Where phosphorus or TEM is not available, the use of spray irradiation may be substituted with good results (Table IV).

Triethylene melamine, similar in chemical structure to the active transformation form of nitrogen mustard, is effective when taken orally and is less toxic than HN_2. TEM shows reduced pharmacologic activity at an acid pH, combines readily with organic material but is relatively stable in an alkaline medium and is usually administered in a fasting state with alkali.[48] Although we have used this method of administration exclusively there has been no reduction in the gastrointestinal disturb-

ances, nor in the variability of effects produced. TEM, like HN_2, is a radio-mimetic drug, its cytotoxic action affecting mitotic division. Hence it is most effective in metabolically active tissue such as bone marrow and neoplasia. Suppression of hemopoiesis with reduction in the peripheral cellular elements occurs, and remissions in erythremia have been produced with both oral and intravenous administration of TEM.[49-51]

Thirty-five cases of polycythemia vera have been treated with TEM over the past few years and certain impressions have been obtained. As with P^{32} the "simple" cases, i.e., those not associated with excessive myeloid hyperactivity, respond best.[17] Similarly, early cases appear to benefit more than patients with a long history of the disease. A good response to P^{32} usually indicates a similar response to TEM but the effect of TEM is much more variable, patients responding to one dose once and not thereafter. Small doses of triethylene melamine may be effective and, because of the cumulative effect and the extreme sensitivity of the marrow, readministration in polycythemia vera should not occur for two months. Remissions are short-lived and rarely exceed six to eight months, although one of our patients maintained normal blood values for two years. Side reactions such as nausea and vomiting limit its use in one-third of the patients. The effective dose can only be arrived at through trial and error although a good starting course appears to be 10 mg. in two divided doses over a two or three day period. When radioactive phosphorus is not available TEM may be used with satisfactory results; however, the variable, short-lived remission necessitates much more frequent blood examinations.

The most satisfactory agent thus far introduced for the treatment of polycythemia vera is radioactive phosphorus.[14, 17, 27, 34, 35, 38]

Radioactive phosphorus, P^{32}, (Table III) when administered either orally or intravenously is initially selectively concentrated to some extent in the nucleoprotein of the mitotically active cells in the bone marrow, liver, spleen and tumors.[14, 35, 52, 53] Eventually, depending on the turnover rate of the tissues, the phosphorus is deposited in the large phosphorus pool of the body, the calcium phosphate of bone. The extent of this initial concentration is dependent upon the total exchangeable phosphorus in the tissue, the rate of utilization of the phosphorus and the rate of growth of new tissue.[35] In polycythemia vera not only does the marrow in its hyperplastic state concentrate more than two to three times its usual share of phosphorus but the eventual deposition of the radioactive isotope

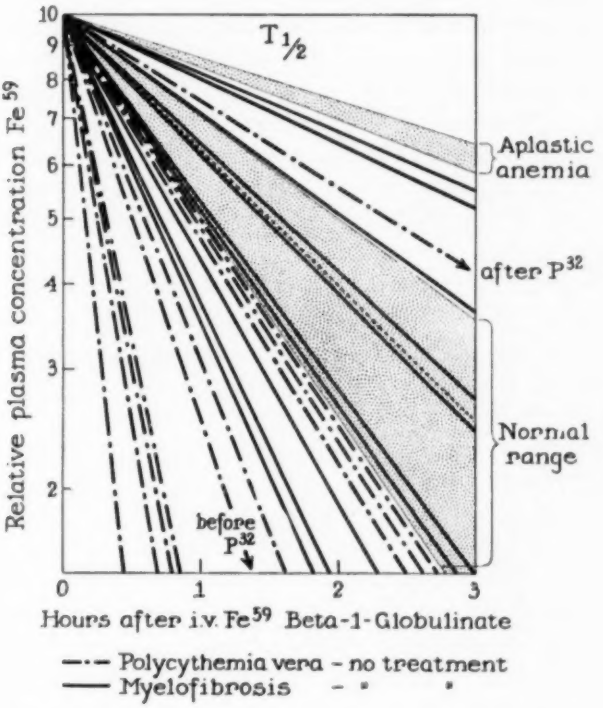

Figure 8: Plasma radioactive iron disappearance in nine patients with polycythemia vera contrasted with the normal and ten cases of myelofibrosis. There is a more rapid clearance of the iron in polycythemia vera signifying increased erythrogenesis. Note the effect of P^{32} in prolonging the half-time of disappearance by the marrow suppressive action of the isotope on erythropoiesis. In myeloid metaplasia the results are variable and approximate the polycythemia values on the one hand and aplastic anemia on the other.

in the bone spicules furnishes added suppressive radiation to the marrow. The desired result of obtaining and maintaining a normal blood picture is achieved by the inhibitory effect of the ionization produced by the beta rays of P^{32} on mitotically active bone marrow cells. This marrow inhibitory effect on erythrogenesis is demonstrated in Figure 8. It has been shown that the half-time of disappearance of intravenously injected radioactive iron, e.g., the time for half of the injected radioactivity to leave the plasma, is a function of erythropoiesis.[1, 2] In normal individuals

FIGURES 9 THROUGH 14: TREATMENT OF POLYCYTHEMIA VERA WITH P^{32} AND/OR TEM (SEE TEXT FOR DISCUSSION OF INDIVIDUAL CASES)

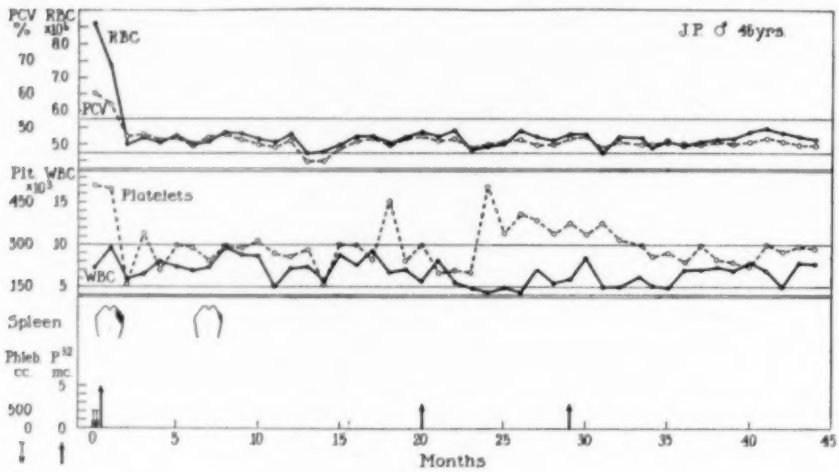

Fig. 9

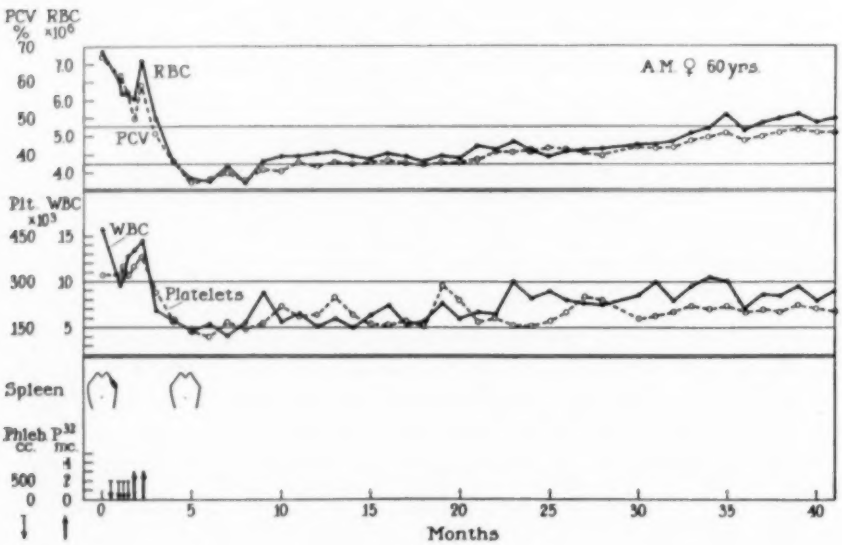

Fig. 10

the half-time of clearance of this iron ranges from seventy to 120 minutes with an average of ninety minutes. Those diseases associated with an empty marrow as in aplastic anemia show a prolongation of the half-time to over 200 minutes, whereas increased erythropoietic activity in the marrow as in polycythemia vera or iron deficiency anemia in a regenerative stage is always associated with an accelerated rate of iron clearance. In nine cases of polycythemia vera tested by this method the half-times ranged from ten to sixty minutes, signifying increased erythroblastic activity in the marrow. The efficacy of marrow suppressive therapy as supplied by radioactive phosphorus in controlling this excessive erythrogenesis is demonstrated by the change in rate of disappearance of the radioiron from a T½ of thirty minutes to a value of 140 minutes, approximating the normal (Fig. 8). With the proper dosage of P^{32} deleterious effects are avoided and the morbidity and mortality associated with untreated or poorly treated polycythemia vera is markedly reduced. Thrombosis and hemorrhage rarely complicate the well treated case of erythremia and it does not appear as if the incidence of leukemia, myelofibrosis and neoplastic disease is increased. Since absorption from the gastrointestinal tract may be irregular and approximately twice the intravenous dose is required orally, we have confined our treatment solely to the intravenous route. Good results, however, have been obtained with oral radiophosphorus therapy.[15]

Figure 9 demonstrates the method of therapy formerly employed by us in most cases of polycythemia vera. This "simple" case of erythremia not accompanied by leukocytosis is the ideal case for treatment with a myelosuppressive agent.[17] Following two venesections totalling 1000 cc. at an interval of three days, the patient was given 5 mc. of P^{32} intravenously. Within two months the platelets and red cell concentration had returned to normal and all symptoms of the disease had disappeared. The maximum reduction in red cells however did not occur until twelve months later. A slow rise in the hematocrit and thrombocytosis and slight recurrence of headaches and dizziness prompted retreatment with 3 mc. P^{32} at twenty months and again nine months later. As can be seen, a hematologic remission has been maintained throughout and splenomegaly has disappeared on minimal doses of P^{32} over a three and a half year period.

More recently we have used 3 millicuries as the initial dose followed in one month by an additional 2 to 3 mc. if necessary. Figure 10 demon-

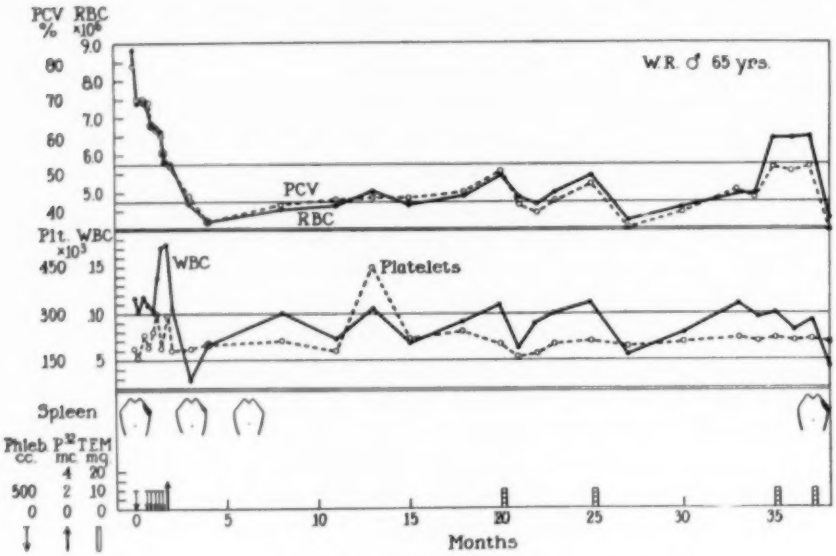

Fig. 11

strates this present method of treatment. Following four venesections at two day intervals totalling 2000 cc. the packed cell volume was reduced from 70 per cent to 47.5 per cent and 3 mc. P^{32} was given intravenously. One month later the hematocrit had again risen to 60 per cent, the white cells and platelets remained elevated and bone marrow aspiration revealed a markedly erythroid marrow similar to the pretreatment sample. An additional injection of 3 mc. was then given. The maximum response occurred two months following the second injection and showed a slight depression of the red cells and platelets below the limits of normal that might have been avoided if a slightly smaller dose had been given at the second injection. Over a period of three and a half years the patient has remained in an excellent clinical and hematologic remission. The blood pressure in this patient has remained persistently elevated in the range of 230/120 despite the excellent response. Little effect on reducing the blood pressure has been noted by us and others following P^{32} or TEM.[14]

The effect of only 3 mc. P^{32} in producing a prolonged remission is illustrated in Fig. 11. Venesections totalling 3000 cc. preceded the dose

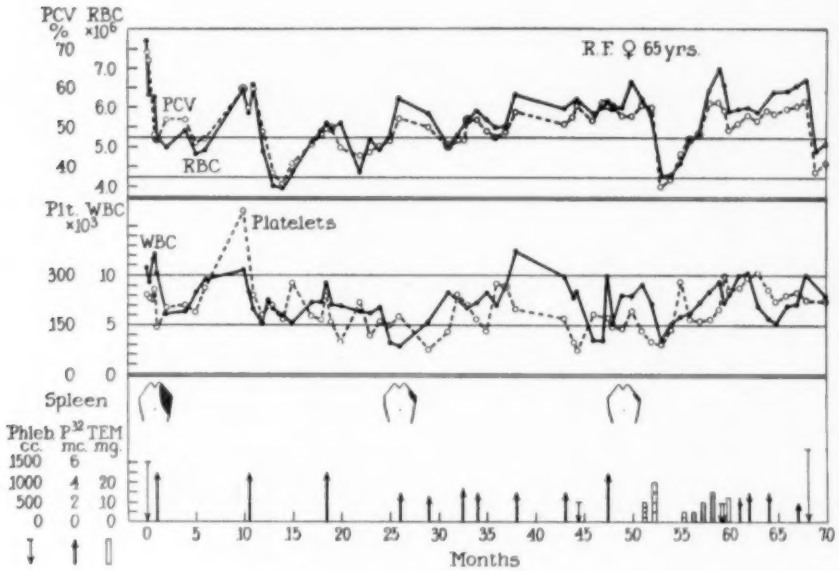

Fig. 12

of radiophosphorus. The maximum response occurred two months later with a slight anemia and leukopenia despite the small dose administered. Note the effect of the venesections in stimulating the white cells. The action of the phosphorus lasted for twenty months when the increasing hematocrit prompted therapy.

TEM was introduced at this time and some of our patients were utilized to evaluate the efficacy of this new drug. The variability in response to similar doses of the drug is well illustrated. The second course of TEM five months after the first produced a greater depression than the initial one and a third course was without effect (Fig. 11). The last dose similar to the others and given after an interval of two months produced a marked drop in the red cells. It is doubtful if this is due to a cumulative effect of the TEM after this period of time. Short-lived remissions, the variability in response and the fear of overtreatment as well as undertreatment following the use of TEM limit one's confidence in the treatment of erythremia with this agent.

Figure 12 demonstrates the marked resistance of some patients to

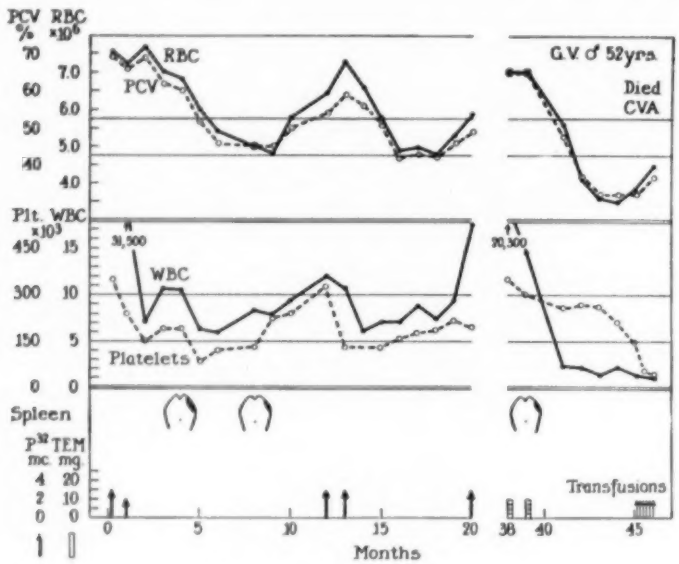

Fig. 13

internal radiation therapy and triethylene melamine. Following three phlebotomies of 500 cc. each, 5 mc. P^{32} produced a maximum response in four months that lasted only two months. Subsequent doses of 3 to 5 mc. at one to five month intervals were ineffective in producing a satisfactory remission. The low level of platelets after the third dose of P^{32} necessitated caution in therapy despite the fact that larger doses of 5 mc. had produced more satisfactory responses. After four years of unsuccessful P^{32} therapy, TEM was tried. The usual initial small doses of 2.5 mg. per day for four days were ineffective but 5 mg. daily doses totalling 20 mg. produced a temporary remission; intolerance to the larger amounts necessitated a reduction to daily 1 mg. doses which also provoked severe nausea and vomiting. Radioactive phosphorus in 2 to 3 mc. doses was again tried with no response. Finally coronary thrombosis occurred and treatment with daily small venesections of 100 to 200 cc. was instituted. The patient is now maintained at normal blood values with frequent phlebotomies and small doses of P^{32} will be administered as needed to maintain normal platelet levels (Fig. 12). In retrospect, myelosuppressive therapy should have been discontinued when the red cell levels could

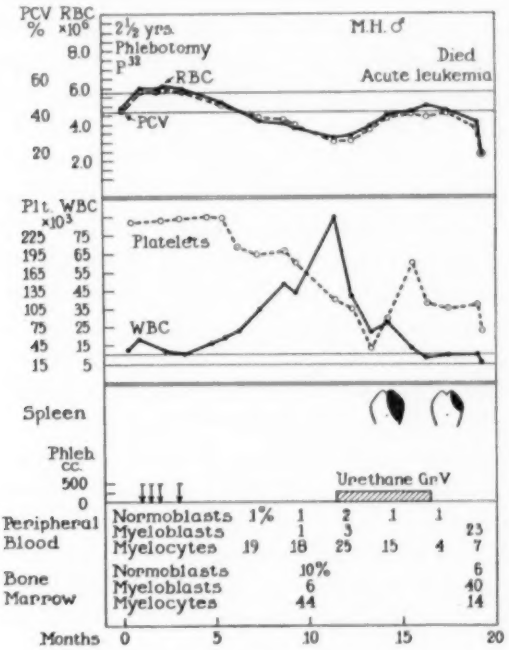

Fig. 14

not be controlled in the face of thrombopenia and leukopenia and venesection instituted as needed.

The danger that accompanies treatment with TEM is well illustrated in Fig. 13. P^{32} was relatively effective in maintaining normal blood values for six to eight months, this despite initial high white cell and platelet levels. An initial dose of 3 mc. P^{32} was followed in one month by 2 mc. of radioactive phosphorus. Retreatment with small doses was necessary twelve months later and again a temporary remission was obtained. After an absence of one and a half years the patient returned and TEM was given with disastrous results. A small dose of TEM, 10 mg. in 2.5 mg. daily divided doses was ineffective and hence one month later the same dose was readministered. A continued fall in all the cellular elements occurred and despite multiple transfusions and antibiotics, a fulminating pneumonia and finally hemorrhage caused death (Fig. 13). Only two 10 mg. courses spaced one month apart were sufficient to precipitate

this fatal episode. At the present time retreatment is never given before eight weeks have elapsed following a previous dose of TEM.

A blood picture indistinguishable from chronic myelocytic leukemia was seen in only one of our cases (Fig. 14). This male, aged fifty-five, had received 3 mc. P^{32} two and a half years previously and had been subsequently controlled by biweekly or monthly venesections. After a polycythemic phase of only three years, the red cells began to fall with a rise in the white cells and the appearance of numerous myelocytes and an occasional normoblast in the peripheral blood. Examination of the bone marrow revealed the myelocytic hyperplasia seen in chronic leukemia but splenic aspiration demonstrated the picture of myeloid metaplasia. Nevertheless the patient was treated as a chronic myelocytic leukemia with urethane for about five months (Fig. 14). A dramatic response in well-being as well as in the blood occurred. The red cells rose and the white cells fell to normal levels and only an occasional myelocyte could be seen on the smears. Urethane was discontinued when the count was normal and symptoms had disappeared. Within a few months, however, the red cells were noted to drop to four million and within one month thereafter the picture of an acute myeloblastic leukemia appeared. Without treatment during the chronic myelocytic stage this patient might have died at that time. With anti-leukemic therapy death was probably postponed until the disease had run its natural course and a maturation arrest in the white cells produced a terminal acute blastic picture. Post-morten examination revealed focal extramedullary hematopoiesis, leukemic infiltrations in all the organs and spotty myelofibrosis. Despite statements to the contrary, myeloid metaplasia with myelofibrosis may be treated with anti-leukemic agents. In four patients we have utilized small doses of splenic radiation with relief of pressure symptoms as well as improvement in the blood picture. Chemotherapy as demonstrated in the case presented above was also successful for a short while in improving the clinical and hematologic status.

Certain principles for the satisfactory treatment of polycythemia vera have been successfully used during the past ten years (Table IV). Initial rapid reduction of the blood volume followed by radioactive phosphorus has given the most satisfactory results. Frequent follow-up visits are essential to maintain normal blood values. Marrow suppressive therapy must be administered cautiously and must be individualized,

particularly when TEM is used because of its greater variability in response. A lack of response in the red cells with depression of the white cells or platelets usually indicates that myelosuppressive therapy should be terminated and venesections utilized thereafter. Elective surgery should not be contemplated unless control of the blood has been established for at least one month.

Although radiation is not the final answer for any treatment, until the etiology of erythremia is known, the marked reduction in morbidity and the ease of administration associated with the use of P^{32} make radioactive phosphorus the treatment of choice in polycythemia vera.

Summary

1. A dynamic concept of polycythemia vera is presented encompassing the various clinical and pathological features encountered during the course of the disease.

2. Polycythemia vera may well be a reticulosis with an initial manifestation in increased erythrogenetic activity; simultaneous and subsequent stimulation of other hematic and non-hematic mesenchymal derivatives will produce the complex syndromes seen in erythremia.

3. The relationship of polycythemia vera and myeloid metaplasia is discussed.

4. The complications in erythremia are directly related to the hypervolemia and panmyelosis.

5. The hemorrhagic diathesis found in polycythemia vera is due to a complex hemostatic defect; elective surgical intervention should thus be avoided unless normal blood values have been achieved.

6. The therapy of polycythemia vera is discussed; radioactive phosphorus remains the treatment of choice in this disease.

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HYPERTENSIVE VASCULAR DISEASE

*Transcription of a Panel Meeting on Therapeutics**

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MODERATOR WILLIAM GOLDRING: The panel today consists of Drs. Herbert Chasis, Edward Weiss, Arthur M. Fishberg and George A. Perera. You have all received slips of paper on which you may write questions. Please deposit them with me.

The first question is directed to Dr. George Perera. *What is the present value of the sodium restricted diet in the treatment of hypertensive vascular disease?*

DR. GEORGE A. PERERA: I think evidence is accumulating that there is a disturbance in sodium metabolism in hypertensive vascular disease and that there is some relationship of the sodium ion to the regulation of blood pressure. However, we have no proof as yet that electrolytes play any true etiological role. Included in the evidence for a sodium disturbance are differences in hypertensive subjects in comparison with normal subjects following the rigid restriction of salt and some prelimi-

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nary reports implying there may be a greater sodium content in the arterioles and muscles of hypertensive animals as compared to normals.

Clinically, we must all admit that sodium restriction does something to some hypertensives. There may be small decreases in blood pressure. There may be improvement in retinopathy and particularly when the retinopathy is advanced. There may be some diminution in heart size, although this occurs only in patients who have some degree of congestive failure. But there are many unpleasant features to rigid salt restriction. Such diets are not very pleasant or palatable and few patients can continue them for a long time. Secondly, there is good evidence that, in the presence of renal damage, salt restriction may depress renal function still further or provoke additional nitrogen retention if already present. In other words, even though we know that sodium plays a part in the overall picture of hypertensives and that its restriction may be associated with improvement in certain areas, there are practical limitations to its use in therapy. Most of us feel that moderate salt restriction should be advocated empirically as part of the regimen of the hypertensive patient. This can be achieved merely by removing the salt shaker, by avoiding salty foods, and by limiting the amount of milk and bread in the diet. Whether this is of definite value cannot be stated at the present time. Rigid salt restriction should be reserved as a therapeutic trial, preferably for short periods, in patients who have more progressive or accelerated disease and who are willing to try it. Caution should be used in any patient who has albuminuria or nitrogen retention.

In summary then, salt restriction forms only a small part of what we can do for the hypertensive subject; when carried to excess it places undue emphasis on a feature of limited value; and it must always be remembered that diets can do harm.

MODERATOR GOLDRING: The next question is for Dr. Weiss. Dr. Weiss is from Temple University School of Medicine in Philadelphia.

What is the present status of psychotherapy in the treatment of hypertensive disease?

Before Dr. Weiss speaks, I should like to introduce him to you by reading an excerpt from something he wrote in 1937, which I think is a classic expression of a point of view in the management of hypertensive patients. In the course of the afternoon he might tell us whether or not in these past fifteen years he has had occasion to alter his opinion. At that time he said, "Now what is done to this poor fellow in an effort

to bring his blood pressure down? Because of an ill-founded idea that protein is responsible for hypertension in kidney disease, he is denied meat and eggs, especially red meat which for some reason is looked upon with particular dread. Then his diet is rendered even more unpalatable by the withdrawal of salt. One would sympathize with this half-starved fellow except that he probably would not be able to eat anyway, his teeth having been removed on the theory that focal infection has something to do with hypertension. Even before this he had sacrificed his tonsils and had had his sinuses punctured because of the same theory. In case some food was consumed, the slight colonic residue was washed out by numerous colonic irrigations, especially during the period when the theory of auto-intoxication was enjoying a wave of popularity. To add to his unhappiness, he may be told to stop work and exercise. Of course, he is denied alcohol and tobacco, as well as coffee and tea, and now to cap the climax of his difficulties, the unfortunate person with hypertension seems about to fall into the clutches of the neurosurgeon, who is prepared to separate him from his sympathetic nervous system."

DR. EDWARD WEISS: The only thing I can add would be that the surgeon is now also prepared to remove the adrenals. Perhaps I can say a word about that a little later.

I think that psychotherapy is not indicated in the treatment of hypertension but it is indicated for most patients who have hypertension. To put it another way, high blood pressure in itself is not an indication for psychotherapy because I know of no evidence that the psyche is responsible for the disease hypertension or that psychotherapy can alter the course of hypertensive vascular disease. On the other hand, I feel quite certain that the symptoms attributed to hypertension frequently arise in a social setting of emotional stress, and that those symptoms are then frequently blamed upon hypertension, which is discovered in the course of the physical examination. Then so often, as you well know, we add to the problem of hypertension by the creation of a blood pressure phobia, and, of course, when that happens there is an indication for psychotherapy and psychotherapy can remove and often does remove many of the symptoms that are attributed to hypertension.

Psychotherapy can be performed by the average physician and indeed it seems to me that in most cases it must be. Some of the profound personality disturbances in hypertensive patients do not yield to even

prolonged psychotherapy and the patient in addition to his high blood pressure has the problem of long continued psychotherapy and the difficulties that often arise out of it to contend with. Of course, every case must be judged individually but in general I would urge that the average physician be prepared to treat his hypertensive patients for the symptoms which are of emotional origin and not confine himself to an effort to reduce the blood pressure.

MODERATOR GOLDRING: In recent months there has been considerable interest in some of the newer drugs that have been introduced in the therapy of hypertensive disease. In formulating this panel it was impossible for us to find anyone near enough to New York City who had had extensive enough clinical experience to make a statement this afternoon, so I suggested to Dr. Chasis that he take the problem. Not having worked with the drugs himself, he hit upon the idea of circularizing by means of a questionnaire all of those in this country, in New Zealand, and in England who had had personal experience with the newer drugs and he is now going to report briefly on the general opinion in this country and in England.

DR. HERBERT CHASIS: As Dr. Goldring said, in preparation for this panel a questionnaire was sent to some fifteen physicians who have had extensive personal experience with the newer anti-hypertensive agents.

My discussion will be a report of their answers to questions that were posed in the questionnaire. The drugs specifically referred to were hexamethonium, ergot and veratrum viride derivatives, and hydrazinophthalazine.

The fifteen who completed the questionnaires were Drs. Lawrence B. Ellis of Boston; Eugene Ferris of Atlanta; Edward Freis of Washington; Keith Grimson of Durham; S. W. Hoobler of Ann Arbor; John B. Johnson of Washington; Ralph Kauntze of London; Edward Meilman of Boston; Milton Mendlowitz of New York; John H. Moyer of Houston; Henry Schroeder of St. Louis; F. Horace Smirk of New Zealand; Maurice Sokolow of San Francisco; Robert Taylor of Cleveland and Robert Wilkins of Boston.

The *first question* asked what hypotensive drugs had been used. All fifteen observers had used hexamethonium, eight ergot derivatives, thirteen veratrum viride derivatives, and thirteen hydrazinophthalazine.

The *second question* asked whether the drugs had been administered to hospital patients only, to ambulatory patients only, or to both. All

fifteen observers administered the drugs to both hospitalized and ambulatory patients. Four reported, however, that they always initially administered these drugs, hexamethonium in particular, during hospitalization by parenteral route and then orally on discharge from the hospital.

The *third question* asked for the type of hypertensive patient in whom the effects of these drugs were being observed. All fifteen physicians had observed the effect of these drugs in benign essential hypertension and in malignant hypertension, ten had observed their effects in nephritic hypertension, seven in eclampsia, and all fifteen in patients in what has been termed "acute hypertensive crises."

The *fourth question* asked, in what hypertensive patient would they not recommend the use of these drugs. Eleven reported that uremia was a contraindication. This opinion was qualified by three who believed that this type of therapy was contraindicated only in presence of marked azotemia; by another who did not continue its use if blood pressure reduction was associated with rise in non-protein-nitrogen blood concentration; and by a fifth who stated that he did not advocate their use in renal insufficiency unless the patient was in the rapidly progressing malignant phase of hypertensive disease and "there is nothing else to do."

Seven observers reported that these drugs ought not to be administered to elderly patients. Five of the seven did not indicate the age they considered elderly, one thought fifty-five years the upper limit, and one thought no patient past the age of seventy years should receive a hypotensive drug.

All fifteen had studied the effects of this type of therapy in the benign phase of the disease, characterized by such terms and criteria as "mild hypertensive," "labile hypertensive," "symptomless hypertensive," "benign with no vascular sequelae," "diastolic pressure less than 120 mm. Hg." Fourteen of the fifteen observers concluded that this type of therapy should not be used in benign essential hypertension.

Ten of the fifteen observers reported that these drugs should not be administered to patients with coronary artery disease as evidenced by anginal syndrome, previous myocardial infarction, or by congestive heart failure. One observer qualified this contraindication to cover a period of not less than six weeks after coronary thrombosis.

Six of the fifteen observers reported that patients with cerebral vascular sclerosis, with and without thrombosis, should not be treated with this group of drugs. One of these physicians thought that encephalo-

pathy was also a contraindication and another that increased intracranial pressure was a contraindication.

The *fifth question* asked whether the drugs were being used for investigation only. Nine of the fourteen who answered this question answered in the affirmative.

The *sixth and final question* asked whether there is sufficient information to warrant the widespread use of these drugs in the treatment of hypertensive disease at the present time. There were seven noes and six yeses; and there were two more yeses with reservations,—that this type of therapy be used only in patients with malignant hypertension, and with proper precautions.

Some general comments were added at the end of the questionnaire and excerpts from these are of interest:

1. Dr. Edward Freis stated that the satisfactory agent has not been found and the drugs now available are stop-gaps.

2. Dr. Eugene Ferris said that these drugs do much more harm than good in the majority of hypertensives. In early benign fixed but nonprogressive hypertensives a vascular neurosis is induced resulting in unnecessary restriction in functional capacity.

3. Dr. Edward Meilman stated that because of the number of adverse effects that may result from combined therapy with hexamethonium and hydrazinophthalazine, these drugs should only be used in malignant hypertension. He also stated that the use of hexamethonium should give sympathectomy its last push into limbo.

4. Dr. John B. Johnson reported that he is not sure that it is in the best interest of patients, with the information available to date on methonium, that this drug should be in widespread use other than in malignant hypertension.

5. Dr. Ralph Kauntze reported his present practice is to use veratrum viride in hypertension of pregnancy and in moderately severe hypertension with symptoms; to use methonium by injection in malignant hypertension, and veratrum or methonium administered parenterally in patients in a "hypertensive crisis."

6. Dr. Ellis reported that his major experience and success has been with Veriloid in "hypertensive crisis," but that there was not much reason for its use otherwise. Long term treatment with it has been almost uniformly unsatisfactory.

7. Dr. Smirk and Dr. Schroeder are using hexamethonium in an

attempt not only to reduce but to maintain the reduction of blood pressure at normotensive levels. Dr. Smirk has treated 200 patients with methonium salts and feels that an effective control of blood pressure level is of advantage to hypertensive patients because he has observed reversal of some of the serious manifestations of hypertensive disease.

Dr. Smirk obtained these results by administering three injections of hexamethonium bromide a day, of whatever dose reduced blood pressure to approximately normal levels. Orally administered methonium or veratrum alkaloids fail in the majority of instances to effect blood pressure control.

8. Dr. Hoobler reported that hexamethonium or protoveratrine is indicated for severe hypertensives with symptoms, particularly those with intractable headache, congestive heart failure, encephalopathy, or with visual failure.

The present opinion of these physicians who have studied these agents can be summarized in this way:

1. Practically everyone reported that one of these hypotensive agents should be used in treating patients with malignant hypertension.

2. There was also general agreement, with one or two exceptions, that these drugs should not be used in the great majority of hypertensive patients with benign essential hypertension.

In other words, in the desperately ill hypertensive patient with an extremely poor prognosis another therapeutic measure is available for trial.

The mode of administration of these drugs was also stressed as a matter of some importance. Oral administration did not impress the majority of these observers as being effective. Some believe that more than one injection a day is necessary to keep the blood pressure at levels that could be considered of therapeutic importance.

All the reporting physicians indicated their appreciation of the dangers involved in the administration of these drugs. It was the opinion of the majority that evidence of advanced disease in the brain, kidneys and heart was a contraindication for their use.

MODERATOR GOLDRING: At this point I am going to ask Dr. Arthur Fishberg to summarize everything that has been said up to this time and to add comments of his own.

DR. ARTHUR M. FISHBERG: I have made a few notes here. I tried to find some point on which I would differ with one of the speakers be-

cause it hardly seems like a panel if one does not differ on any point, but I was unsuccessful.

I think from what Dr. Perera brought out that it must be clear that sodium restriction, which is the one measure I think is almost universally used in hypertensive patients, is not causal treatment. All it does is in some way affect the homeostasis of the circulation so that the blood pressure is maintained at a lower level.

I think the fact that after bilateral complete adrenalectomy, when maintaining the patient on small doses of cortisone the blood pressure may still be high is in itself proof that there is no causal disturbance of sodium metabolism. Nevertheless there are a certain number of patients, as Dr. Perera brought out, who do respond to maximum sodium restriction but unfortunately that response is not only to maximum restriction but to rest and such psychological influences as go with the sodium restriction. Thus, it is often hard to say what is lowering the blood pressure when it is lowered. I am not sure that I am in agreement that moderate sodium restriction, that is to say when you have about a gram or a gram and one-half of sodium in the urine in twenty-four hours, is actually of value. I formerly thought so but now I have doubts, that is, unless there are symptoms of heart failure.

I am very glad that Dr. Weiss brought out the point that we have no proof that essential hypertension ever actually originates in the psyche. That belief is coming more and more to the fore and among the public it is getting to have very wide acceptance. What Dr. Weiss stated comes to this, that if a hypertensive patient is one who would be benefited by psychotherapy, even if he did not have high blood pressure, by all means he should have it, but there is no indication for any deep psychological exploration merely because the patient has high blood pressure. One must bear in mind that formal psychotherapy can sometimes do harm and not only good. It often does a great deal of harm to the patient's pocketbook but I don't mean only that. I mean there are patients who after psychotherapy, perhaps not administered in the most judicious way, have more psychological symptoms than they had before.

Dr. Chasis surveyed the field of the newer drugs which are becoming more and more popular. I think you are all being bombarded, almost daily, from one pharmaceutical house or another. These drugs are being pushed very strongly, much beyond their actual merits. However, I think this much may be said, in hexamethonium at least, we have a drug

with which we can almost always reduce the blood pressure. But it may do some terrible things to the patient. He may be much worse in spite of reduction in blood pressure. You cannot be too careful with the drug. I myself have had one fatality in a patient treated with hexamethonium who really had had only very minimal symptoms of coronary insufficiency. In fact, we were only certain of it after what ultimately happened. From the course of events in that particular case I don't think there was any doubt that it was due to the use of the hexamethonium. So you have to be very careful in using it and be certain that the patient has no evidences of impairment of blood flow either to the heart or the brain.

There is one circumstance though, in which hexamethonium and particularly Veriloid represent a real advance and that is in the treatment of hypertensive encephalopathy, whether that hypertensive encephalopathy be incurred in the malignant phase of essential hypertension, in glomerular nephritis or toxemia of pregnancy. In the hypertensive encephalopathy which is dignified by the name of eclampsia but actually pathogenetically does not differ from other forms of hypertensive encephalopathy, the use of intravenous Veriloid—I have had no opportunity to use the intramuscular preparation which has been brought out—gave startling results and there is no question at all that it represents a great aid in many of these cases.

MODERATOR GOLDRING: This is a good time to ask other members of the panel if any one of them wants to disagree with anything that has been said.

DR. CHASIS: I would like to say a word about the problem of hypertensive crisis or acute encephalopathy. In the questionnaire the term was used to indicate an episode of sudden symptomatology predominantly cerebral, synonymous with acute encephalopathy. It was interesting to see how difficult most of the reporting physicians found indications for and contraindications to the use of these hypotensive agents. It was generally agreed, as Dr. Fishberg said, that they should be used in patients in hypertensive crises but practically all warned against the great danger of using them in patients with cerebral vascular accidents.

As you all know, the differential diagnosis between acute encephalopathy and cerebral thrombosis or hemorrhage is frequently difficult and only time establishes the correct diagnosis. I would like to issue a

word of warning about administering these drugs to hypertensive patients with marked cerebral symptomatology unless one is certain that he is dealing with a reversible phenomenon and not with thrombosis or hemorrhage.

MODERATOR GOLDRING: *Are there any further comments on what has been said so far?*

DR. WEISS: I should like to ask, should salt be restricted in every patient with elevated blood pressure?

DR. PERERA: May I just clarify one feature in my previous remarks. Very frequently, in the handling of a hypertensive patient, I restrict salt to some extent. But I must admit that my reasons are empiric, in the direction of experimental evidence, but without established foundation. I do it in part as something to do which is easy to do, which does not produce invalidism, and which is not psychologically too handicapping. It cannot be recommended as a routine. But I would certainly agree that our greatest error in management is in creating invalidism, fear and anxiety rather than doing our best to allay it.

MODERATOR GOLDRING: Dr. Chasis, here is a question for you, one that you can answer for me too: *What is malignant hypertension? You indicated I think from the questionnaires you received that malignant hypertension was one indication for the use of these newer drugs. What is it?*

DR. CHASIS: We don't like or use the term. The criteria for its diagnosis are somewhat subjective and it would not be surprising if the five of us, seeing the same patient might differ, three thinking malignant hypertension and two not. The diagnosis of malignant hypertension is usually made on the basis of the presence of marked diastolic hypertension and neuroretinopathy in a relatively young person in whom the physician believes that the pace of the disease is accelerated and in whom death will occur in a matter of months. We find it difficult in some patients to be certain that the accelerated pace will be maintained. Another difficulty that arises when one uses the term "malignant hypertension" was manifest in the answers and discussion of the questionnaire cited earlier. Although all agreed that patients with malignant hypertension, so-called, should receive hypotensive drugs, eleven of the fifteen felt that uremia was a contraindication and we all know that in malignant hypertension it is nearly impossible in some patients to set off in time the pre-uremic from the uremic phase. There are many patients

who appear to have innocent renal findings and who very rapidly develop evidence of marked renal functional impairment. It might be dangerous therefore for some patients with "malignant hypertension" to receive a hypotensive agent. Hypotensive drug therapy may contribute to the rapid course of uremia in malignant hypertension.

MODERATOR GOLDRING: Dr. Fishberg, before you speak—I may be anticipating you—if it is difficult, and all agree that it is difficult, to make the diagnosis of so-called malignant hypertension before renal impairment has occurred; if it is almost impossible to distinguish between acute encephalopathy and cerebrovascular accident, at the onset or as soon as possible thereafter when it is said the treatment is indicated; and the drugs are not to be used in the benign form of hypertension; and since you have indicated you might favor Veriloid, when *would* you use it?

DR. FISHBERG: I believe there are a good many cases in which you can diagnose hypertensive encephalopathy with a very high degree of probability and I certainly would use it in those. For instance, in glomerular nephritis cases in the young, one very often sees the acute rise in blood pressure develop, terrific headaches, swelling of the disc, high cerebrospinal fluid pressure. That is quite a common syndrome akin to what is called eclampsia in pregnancy and one sees the same picture in the malignant phase of essential hypertension and one feels that the patient has edema of the brain; this is one of the circumstances in which I would use it, always with the greatest caution. One cannot be too careful in giving it. The blood pressure must be taken continuously on the other arm. When the patient has entered the malignant phase of essential hypertension as documented by the high diastolic pressure, terrific headaches, blurring of the disc margins, when renal function is still intact (the urine may be negative at that time) this type of case I believe sometimes warrants an attempt with these drugs.

If I may, I should like to say a few words on the concept of malignant hypertension. The way I view it is this: of course it is only one conceptual delimitation. Various clinical pictures occur in hypertensive diseases. However, there are certain clinical pictures in which it seems highly probable that actual bursting pressure within the vessels is creating certain symptoms, certain manifestations, one of which is necrosis of vessels in the kidney, another edema of the brain, and a third, in my opinion, what is called hypertensive retinopathy. I personally use the

words "malignant hypertension" for those cases of hypertension, whatever the cause, in which these features that I believe are due to actual high intravascular pressure are operating and for more precise diagnosis I like to use the expression "malignant phase" of glomerular nephritis,—"malignant phase" of essential hypertension. One can say "malignant phase" of toxemia of pregnancy when the patient presents the picture that is designated as eclampsia. That is my conception of the condition. So that whenever a method of treatment is proposed, such as the Kempner rice diet, sympathectomy, and now these new drugs, any of which will lower the pressure, and which sometimes also result in a recession of this particular clinical picture that I would like to designate as the malignant phase of the particular disease.

MODERATOR GOLDRING: *Dr. Fishberg, that brings us to a question addressed to you: What is the present status of the rice diet?*

DR. FISHBERG: I will give you my opinion of the present status. I am afraid it would not agree with Dr. Kempner's opinion at all or with many others. Apparently the one essential feature of the rice diet is sodium restriction and the rest is what you might call window dressing. There have been a number of people who seem to have demonstrated that if you bring the blood pressure down by means of the rice diet and add protein to that diet—and I am sure the same thing would apply if you added fat to that diet—that the pressure will stay down if it has been brought down by the original rice diet. I would like to hear the opinion of other members of the panel on that.

MODERATOR GOLDRING: George!

DR. PERERA: I agree with that completely. There is excellent evidence now that the only virtue in the rice diet in hypertension rests in its low sodium content.

MODERATOR GOLDRING: *Ed, will you comment on this diet?*

DR. WEISS: Only this, that I think when people have their attention focused too much on a weird diet that the harm that is done to them by this obsession is often worse than what is produced by the disease. I have seen a number of patients who have become enslaved by this diet and they suffer in my opinion a great deal more because of their obsession with this diet than if they were allowed to go on with their benign essential hypertension.

Before the afternoon is over I would like to know from the members of the panel whether they always treat patients with high blood pressure

for the high blood pressure. In other words, should every patient with high blood pressure be told that he has high blood pressure and should everyone be treated? I would like very much to get the opinion of the panel members.

MODERATOR GOLDRING: *Herbert, will you comment on that point and the rice diet?*

DR. CHASIS: Our experience with the rice diet was disappointing. We observed no great falls in blood pressure, and we had rebellious patients on our hands after months of strict enforcement and policing during hospitalization. When we took those considerations in mind and combined them with the adverse effects on renal function (the fall in rate of glomerular filtration, renal blood flow, and tubular excretory capacity), we concluded we would not advise the rice diet. We do restrict salt in the presence of heart failure.

We believe treatment of the hypertensive patient should not be directed at the blood pressure. We attempt to relieve symptoms. We discourage any interest in the absolute level of blood pressure.

Dr. Fishberg and I disagree on the significance of the absolute level of blood pressure elevation. Neither of us has direct proof and so he is just as apt to be correct as we are. We are not convinced that the level of blood pressure influences the course of the disease in the great majority of hypertensive patients.

MODERATOR GOLDRING: Dr. Fishberg.

DR. FISHBERG: I should like to make one comment on what Dr. Chasis just said. A few years ago I took out a lot of old history cards and looked at the diastolic pressures of those patients, whose pressures had all been taken by me, and from what I saw there was definitely a greater mortality in those with the higher diastolic pressures. I realize that the absolute height of the pressure has not an invariant correlation with the outlook but each ten points of higher diastolic pressure in a number of patients carries with it a higher mortality, and particularly a higher incidence of the malignant phase from what I observed.

I should like to underline, while I am at it, what Dr. Weiss said. I feel that a high proportion of the individuals who are found to have high blood pressure in a routine examination should by no means be treated for high blood pressure.

MODERATOR GOLDRING: Dr. Chasis and Dr. Fishberg have anticipated the schedule a little, and I should like to emphasize a vital point and that

is the relationship of the level of blood pressure to the progress of the vascular disease. *George, we might just as well complete it now by asking you what you think about the relationship between the level of the blood pressure and the progress of the vascular disease.*

DR. PERERA: That is easy. I am going to step right between the previous speakers and take a stand that perhaps brings them more closely together. We have followed a large group of hypertensive patients for a mean period of about sixteen years. Granted that one can always quibble and say that the blood pressure levels taken at one time of the day are not the same as recorded one minute or an hour later, or at night, we have concluded that one must separate statistics from the individual. If all those with higher diastolic pressures are grouped together and compared to those with lower diastolic levels, the average patient with the higher diastolic pressure does not do as well. Individually, however, we have seen diastolic values never below 150 for a period of ten consecutive years, never below 130 for a period of twenty consecutive years without progression of the disease. I think in the practice of medicine we must be very careful in using one reading or several readings as proof positive of what will happen to one patient. Although statistical correlations exist, the casual blood pressure, as obtained in an office or in a clinic, bears little correlation to either the outlook on life or the development of congestive failure, retinopathy, renal complications, etc. It is very difficult to bet on one patient, in whom the odds are invariably zero or 100, but it is possible to generalize.

MODERATOR GOLDRING: Dr. Perera, to impose myself once more, you are saying something with which we all agree; that the sicker hypertensive patients have the higher blood pressure levels. *The question is: is the patient sicker because his blood pressure level is higher?*

DR. PERERA: My own feeling is no, and the reason I say no is because we have found many discrepancies between the degree of sickness, the rate of progression and the level of blood pressure. That is a minority point of view but I would like to back it up by an observation that I think is pertinent. We have followed a small group of hypertensive patients in whom the hypertension disappeared. It disappeared for months, or a year or more, because of a myocardial infarction, a cerebrovascular accident or because of the development of unrelated valvular disease. In some of these patients we have seen progression of some of the complications of hypertension such as retinopathy. It becomes diffi-

cult for me to feel that it is the blood pressure alone which caused the retinopathy or the blood pressure alone which caused the hypertrophy of the heart. It becomes even more difficult when one sees marked, rapid enlargement of the heart with relatively little hypertension, and other patients with long-sustained, high hypertension and no increase in heart size over periods of years and even decades.

MODERATOR GOLDRING: We will now switch to the surgical aspects of the treatment of hypertensive diseases. The first question is directed again to Dr. Perera: *What is the present status of unilateral nephrectomy on the natural history of hypertensive disease?*

DR. PERERA: In my opinion unilateral renal disease is an uncommon but not a rare condition. Infrequently it is associated with hypertension, but I am sure in many of those patients only as a coincidence. However, on very rare occasions, unilateral renal disease is responsible for hypertension, in that removal of the diseased kidney will "cure" the patient not for one year but for seven or ten. That is a very rare condition but a pleasant one if found, because if the offending kidney is removed the progressive disease comes to an end.

In going back over those patients who are "cured" by the removal of a sick kidney and by comparing them with patients in whom the operation is performed because of unilateral renal disease and hypertension but without cure, certain things appear which may be of diagnostic help. Where unilateral renal disease causes hypertension, in our experience, the course of the disease is an accelerated one; the hypertension is of short duration; retinopathy and headaches are common; high diastolics are common; and nearly always the pathology is shown to be either a definite vascular insult to the kidney or an inflammatory lesion such as pyelonephritis.

On the other hand, a more common experience is to encounter a hypertensive patient in whom a small kidney or a congenital abnormality on one side is found and an operation performed without relief of the hypertension. In retrospect, these patients usually had their hypertension for a longer period of time; it was not usually of the accelerated or malignant variety. In all probability these patients represent the coincidence of a congenital or acquired abnormality and an unrelated hypertensive vascular disease.

Practically then, given the patient with albuminuria, in whom there is no documentation as to cart and horse, there is a reason for doing an

intravenous pyelogram and looking for the possibility of unilateral renal disease. For practical purposes, however, unless the course of the patient was relatively short and rapidly progressive and unless the pathology on clinical grounds appears to be that of infection, the chances of cure by nephrectomy are very, very slight.

One final point, in my experience essential hypertension does not begin after the age of forty-eight or fifty. On repeated occasions now we have observed patients known to have had a normal blood pressure who developed hypertension after the age of fifty. For whatever it is worth, every one of those patients had a cause demonstrated for their hypertension other than hypertensive vascular disease. Sometimes it was periarteritis or a collagen disease but the great majority proved to have unilateral renal disease and were cured apparently by the removal of the offending kidney. The sudden appearance of an unexplained hypertension after the age of fifty should make one more suspicious of a known cause of hypertension and its possible cure.

MODERATOR GOLDRING: *Dr. Fishberg, will you comment briefly on sympathectomy?*

DR. FISHBERG: I think my comments can be much briefer than they might have been a few years ago. I don't think that the stock of sympathectomy has been going up in recent years as we had more and more opportunity to observe the patients. The proportion of patients with essential hypertension in whom sympathectomy is indicated seems to be extremely small. I don't think it is much more than one in fifty. The indications in general are hypertension in an individual below the age of fifty, who is definitely deteriorating despite every non-surgical therapeutic measure and in whom there are no arteriosclerotic complications. When you try to satisfy both those criteria you are down to a very small number of patients. However, among those patients there are some who do respond brilliantly for a matter of at least five years and sometimes ten years, in whom the symptoms clear up completely, in whom the retina clears and in whom the pressure runs at a decidedly lower level, but I would like to stress that sympathectomy is indicated in only a few very sick hypertensives.

MODERATOR GOLDRING: *Dr. Weiss, what is the present feeling about bilateral complete adrenalectomy?*

DR. WEISS: Having just referred my first patient for that purpose I can hardly speak from personal experience. But I just called up Dr. Zin-

tell of the University of Pennsylvania, who works with Dr. Wolferth and does the surgery on those patients, and he brought me up to date on their experience. They have operated upon eighty-nine patients whom they have followed for an average period of thirty-three months. They are now doing bilateral complete adrenalectomy. It is a subcostal operation, one side at a time, with an interval between operations about the same as sympathectomy. They find a little less incapacity from the operation than follows sympathectomy. Their mortality is slightly higher, 2.9 per cent for the operative procedure but they have been dealing with very sick people. The operative morbidity is less. They have been using the operation on the type of severe progressive disease that we have discussed here—the rapidly progressive hypertensive disease with high diastolic pressure, cases that have been sympathectomized and then regressed, and some patients with intractable headache and other symptoms that could not be relieved. The statistics that he gave were as follows: in 22 per cent of this group they re-established normal blood pressures—the pressure both in recumbency and in the standing position has approached normal levels. In 29 per cent there has been a significant reduction of blood pressure in the standing position but not lying down. In 33 per cent there was no change in blood pressure levels but removal of symptoms or improvement of symptoms and 16 per cent were regarded as failures. The after-treatment consists of cortisone and salt and in certain cases the use of DOCA as well. He has cited a number of individual instances to me in which a remarkable degree of recovery has occurred for a long enough period now to seem significant.

If I could say just one word regarding sympathectomy, the most brilliant result I have seen occurred in a patient with rapidly progressive hypertensive disease, who had sympathectomy a little more than five years ago and had a perfectly normal blood pressure, followed carefully for a period of five years. There was complete restoration to usefulness again but he died early last November of coronary occlusion. It brought home to me what has been emphasized here that even though we modify the blood pressure, so often the vascular disease apparently goes on.

DR. FISHBERG: May I say one word apropos of that? Dr. Weiss, do you think that the case you just cited reflects against sympathectomy? After all a man who had been cured of carcinoma of the stomach five years ago might have had a coronary occlusion, which is a pretty com-

mon thing. I will admit this that the incidence of arteriosclerosis in hypertensives is far higher than in the control population, just as it is in diabetes, but I think that most of the evidence points to arteriosclerosis and hypertension pursuing independent courses though either may aggravate the other.

DR. WEISS: No, I certainly would recommend sympathectomy for that patient again or perhaps now adrenalectomy because I don't know what else to do for this rapidly progressive disease.

MODERATOR GOLDRING: *Dr. Chasis, will you summarize what has been said regarding the surgical treatment of this disease?*

DR. CHASIS: It is apparent that one bright aspect in the treatment of hypertensive patients is nephrectomy. Sympathectomy and adrenalectomy are desperate maneuvers in desperately ill patients, with the family and the physician eventually becoming desperate. The detection of patients with unilateral disease, as Dr. Perera has indicated, is the responsibility of the examining physician and a difficult responsibility to discharge. The incidence is extremely rare. Dr. Homer Smith estimated that possibly one in a thousand hypertensives may be a candidate for nephrectomy and that is probably a high figure. The fact that the patient is a candidate does not mean that the operation will succeed. In some 250 nephrectomies performed in patients in whom it was thought that the removal of a diseased kidney might result in lowering of the blood pressure to normal, only one out of five resulted in the cure of the hypertension. The criteria that we use, in addition to those that Dr. Perera has indicated—and his contribution last year was a very important one—are, first, that the diseased kidney have practically no function. We think it is incorrect to deprive a hypertensive individual of any significant degree of functional renal tissue which later in life may sustain him; second, that the contralateral kidney have normal function; and third, that there be urological indications for removal of the diseased kidney, such as pain, stone or infection. About ten years ago Dr. Weiss saw a patient who had a recent onset of fairly marked diastolic hypertension and unilateral renal disease. We measured renal function in the separate kidneys and discovered there was no function in the left, a chronic, atrophic, pyelonephritic contracted kidney, whereas the right had supernormal function. The left kidney was removed. Dr. Weiss informed me just before this meeting that two years ago, nine years post-nephrectomy, the patient still had hypertension. We conclude that

failure to cure this patient of hypertension indicates that the diseased kidney was not the cause of the hypertension. Nor can it be argued that the remaining kidney is responsible on the basis of alterations in hemodynamics because postoperative observations revealed the remaining right kidney to have normal ratios of renal blood flow, filtration rate, and maximal tubular excretory capacity. It is our present feeling that it is the responsibility of the examining physician, when there is a clue in the history, in the pyelogram, or in the urine to detect unilateral renal disease and to decide whether the patient is a candidate for nephrectomy.

The interest in sympathectomy is on the wane. In the first place the newer drugs are said to perform a "medical sympathectomy" and it is much simpler to administer a drug than to operate. The second reason is the difference of opinion that exists in criteria for the selection of patients for surgery. It is the opinion of some that the best kind of patient to operate on is the one with early labile essential hypertension. On the other hand, there are other physicians who don't advise sympathectomy until the prognosis is extremely poor. Some physicians believe that the presence of marked congestive heart failure is a contraindication to sympathectomy whereas Chavez in Mexico has a series of patients with marked congestive heart failure in whom the operation resulted in clearing of the heart failure. A third reason for loss of interest in sympathectomy is the high incidence of failures, both immediate and late.

Total bilateral adrenalectomy is in the experimental stage and not to be recommended as an accepted mode of therapy.

MODERATOR GOLDRING: We have time now for a few short questions. *Dr. Perera, this is addressed to you: What is the effect of alcohol on existing hypertension?*

DR. PERERA: That is very difficult to answer because ordinarily one does not titrate the blood level of alcohol with the blood pressure and make pertinent scientific findings. Speaking in general terms I think there are many physicians who would regard alcohol in small dosage in terms of its sedative and vasodilator effect. Thus we have felt that, for those who like it, small amounts may be beneficial rather than harmful. Obviously alcohol in excess would be harmful to the hypertensive patient.

MODERATOR GOLDRING: Dr. Weiss, this is a question addressed to you: *You speak so much of psychotherapy. Explain the general practitioner's*

approach. In detail in two minutes!

DR. WEISS: I think in general one can say that you have to be very cautious about interpreting symptoms in patients who have high blood pressure and attributing them to the high blood pressure. So often there is another cause for the symptom, and that is what ought to be treated. When we put too much emphasis on the blood pressure we simply create more of a problem for the patient, and produce more symptoms. If we inquire into the life situation of the patient who has high blood pressure, we will frequently find that the symptoms arose during a period of emotional stress. If we can do something about relieving his tensions, either by helping him to see his problems differently or by changing his environment a little or both, we can often help him with his symptoms even if we cannot take away his hypertension.

MODERATOR GOLDRING: Now briefly in order to get in as many questions as possible. *Dr. Fishberg, What do you think of the effect of excess fluid in hypertension?*

DR. FISHBERG: I don't think it does any harm at all. Of course, the word "excess" means many things. A few years ago Miller of Chicago did some experiments in which he had a patient drink ten liters of fluid in twelve hours and his pressure went up. I was not referring to that.

MODERATOR GOLDRING: Nor the questioner, I am sure. *Dr. Chasis, How do you reconcile the moderation as advocated here in sodium restriction with the fact that some reduction in blood pressure is achieved by the rice diet? In other words, is it the low salt or is it the rice in the rice diet that reduces the blood pressure?*

DR. CHASIS: I think Dr. Perera and Dr. Fishberg have answered that and we are in agreement that it is the restriction of sodium and not the rice diet that effects the moderate reduction in blood pressure.

MODERATOR GOLDRING: I think we would all agree with that. *Dr. Perera, Do you restrict physical activity in benign essential hypertension?*

DR. PERERA: No.

MODERATOR GOLDRING: *Dr. Fishberg, Hypertensive patients have been asked to give blood to other people who need blood transfusion. How often can they give the blood and how much?*

DR. FISHBERG: I would say the situation is no different than with the normotensive individual.

MODERATOR GOLDRING: *Dr. Weiss, Could two tablets of methonium*

a day in a hypertensive patient with a blood pressure of 240/160 be responsible for fatal cerebral vascular accident? The drug was given over two weeks. The patient was a female, age sixty-eight.

DR. WEISS: I cannot answer that.

DR. FISHBERG: I don't think it would cause cerebral hemorrhage but one could conceive by hexamethonium causing a cerebral infarction if it dropped the pressure abruptly.

MODERATOR GOLDRING: The dose seems quite small.

DR. FISHBERG: I don't believe so but it is conceivable.

DR. PERERA: To reassure the questioner, in the course of a week's therapy some tolerance would have developed,—another one of the difficulties of using hexamethonium. I would doubt very much that it was the medication that produced that particular trouble.

MODERATOR GOLDRING: *Dr. Chasis, what is the significance when the blood pressure taken from both arms varies, both in systolic and diastolic?*

DR. CHASIS: There is a normal variation of 10 to 15 mm. of mercury in the two arms and no particular significance is attributable to such differences. Variations in excess of this indicate that disease of the aorta and its branches should be sought.

MODERATOR GOLDRING: *George, What is the relation of pheochromocytoma to hypertension?*

DR. PERERA: As you know, a pheochromocytoma can cause hypertension of two types, paroxysmal or a sustained form which can mimic hypertensive vascular disease.

MODERATOR GOLDRING: *Dr. Fishberg, When would you perform the pharmacological tests for pheochromocytoma?*

DR. FISHBERG: I don't think they should be performed in all hypertensive patients by any means. I would only perform them in cases notably of paroxysmal hypertension, which are for that reason thought of as a possibility, or if there was some unusual feature in a continuous hypertension. In other words, every fellow who is picked up with a blood pressure of 170 in a routine examination feels practically well, need not be tested with one of the drugs.

MODERATOR GOLDRING: Two final questions, for each of the panel members for a one minute survey. *The first is: What is the value of the reduction of weight in the obese hypertensive?*

DR. PERERA: That is more difficult than it sounds. I am sure that weight reduction bears little or no relationship to blood pressure or the

disease but that it does increase the reserve of a patient if he or she has the beginnings of congestive failure. The story that hypertension disappeared in certain famine areas is controversial. I would like to suggest two unknowns because only by thinking about them can we learn the ultimate answer. On the one side is the possibility that weight reduction would have a bearing on the development or rate of progression of arteriosclerotic complications. No proof of this exists as yet. To make it harder, and on the opposite side, most of us have been under the impression that the obese labile hypertensive seems to do somewhat better than the thin one. Until we know more, the improvement in cardiac reserve and the possible bearing of obesity on arteriosclerotic complications would make weight reduction a wise maneuver in the hypertensive patient.

DR. FISHBERG: I think if a hypertensive is notably obese he should bring the weight down but one of the cliches in hypertension has been that reduction of obesity helps the patients a great deal and except under the circumstances mentioned by Dr. Perera, when they are short of breath, have some indications of heart failure, I don't think it is very important.

DR. WEISS: I agree with what has been said.

DR. CHASIS: I think the reason for the cliche may be that the basis for some of the older statements arises from studies in which a standardized cuff was used. On an arm of large diameter, the average size cuff will give a false high reading. In an arm of small diameter, the average size cuff will give a false low pressure. There may have been mistakes in dividing the groups into normo and hypertensives. Ancel Keyes has studied the relationship between weight, body size, surface area, cardiac output and intra-arterial blood pressure and found no relationship between increasing weight and increasing mean intra-arterial pressure in normal young adults.

MODERATOR GOLDRING: In connection with that, Bordley and Ragan made the same observation. They showed that the direct blood pressure readings simultaneously compared with the indirect blood pressure standard cuff reading showed a discrepancy in terms of increased blood pressure both systolic and diastolic with the indirect method, in arms with larger than usual circumference; indicating that some of the increase of blood pressure in the obese is an illusion, that it is due to the large size of the arm and the relative smallness of the cuff rather than a direct

relationship between obesity and hypertension.

Now the last question—the question has been asked a number of times here—is: *What is the present status of the low cholesterol diet in the treatment of atherosclerosis?* Can we answer it in about one minute each?

DR. PERERA: Are we referring to atherosclerosis or to complications of hypertension?

MODERATOR GOLDRING: Either way.

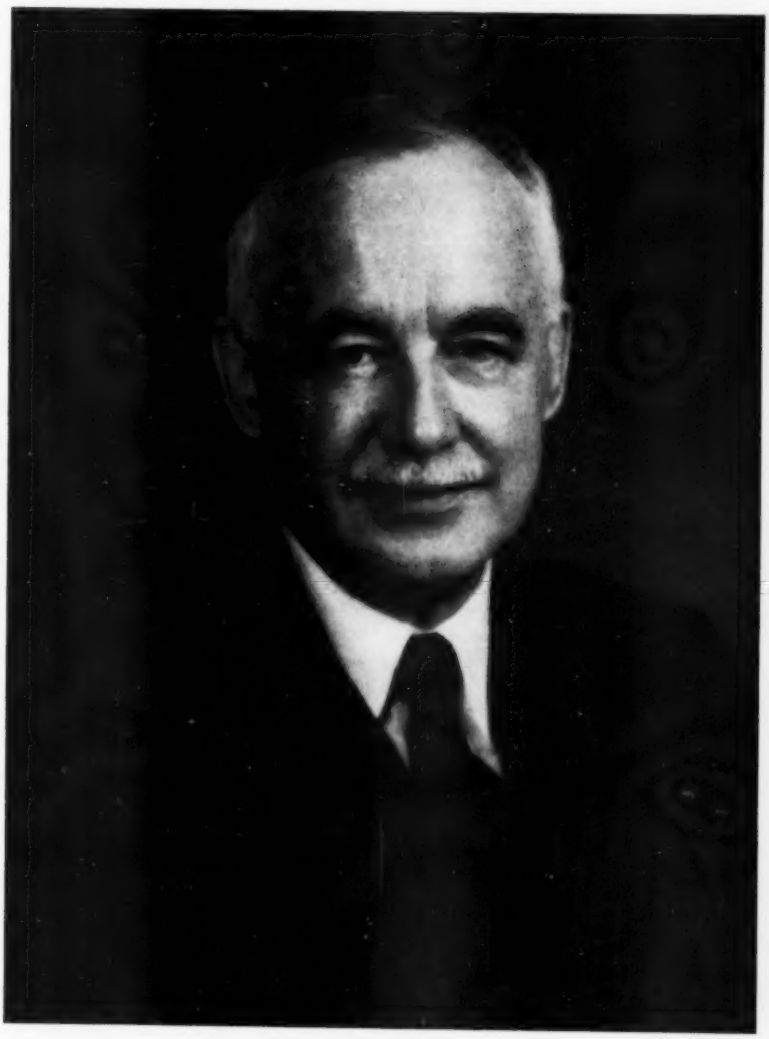
DR. PERERA: The ideal therapy for the hypertensive would be to find the cause and cure it. Until that objective is reached we should be interested, not just in lowering the blood pressure but in those factors responsible for the development of the organic complications including the arteriosclerotic process. Practically, though, we are faced with the problem that unless diets are made so low in fat and cholesterol, they have no effect on serum cholesterol levels. Unless a diet contains less than 200 mg. of cholesterol and 20 gm. of fat, it appears to be without effect. Such diets are unpalatable, unpleasant and difficult for most people. Perhaps again it is something that one might attempt in an occasional patient who wants to try it, but to my knowledge we have no proof yet that extremes of dietary juggling will alter each individual's cholesterol pattern or truly prevent or reverse the arteriosclerotic complication.

DR. FISHBERG: I am in complete accord with what Dr. Perera has said. It seems to me despite the very interesting work of Dr. Gofman and his group, there is still no definite proof that low cholesterol diets affect the incidence of atherosclerotic disease.

DR. WEISS: I think fat people ought to reduce by means of sensible diets regardless of what they have.

DR. CHASIS: No facts.

MODERATOR GOLDRING: Thank you.



ARCHIBALD MALLOCH, M.D.

1887 – 1953

Archibald Malloch, M.D.

1887 – 1953

Dr. Archibald Malloch, Librarian Emeritus of The New York Academy of Medicine, died on September 19, 1953 at the age of sixty-seven. He had been Librarian from 1925 until his resignation because of ill health in 1949.

Dr. Malloch was born in Hamilton, Ontario, August 10, 1887, the son of Dr. Archibald E. Malloch and Mary Frances Reynolds Malloch. His father, a leading surgeon of the region, had served as Lister's House Surgeon in 1868 and was a close friend of Sir William Osler.

After graduating from the Faculty of Arts, Queens University, with the degree of B.A., Dr. Malloch entered McGill University where he received his M.D.C.M., from the Faculty of Medicine in 1913. Further training as medical intern and resident pathologist and bacteriologist was interrupted by World War I, when Dr. Malloch joined the Canadian Red Cross. He was first assigned to the Friends' Ambulance Unit at Dunkirk in October, 1914, having crossed the Atlantic on the Lusitania's last trip before her sinking. In 1915, Dr. Malloch served at Depage's Hospital at La Panne. In July, 1915, he opened a new hospital for officers at Burley-on-the-Hill, Rutland. This was for years the home of the Finch family. Here, at the suggestion of Sir William Osler, he began work in his spare time, on *Finch and Baines, a Seventeenth Century Friendship*, the research being done at the Bodleian Library. The book was published in 1917.

In 1916, Dr. Malloch was transferred to Alford House, London, which had been set up as a hospital for officers. In the spring of that year he joined the newly formed McGill Unit being stationed at Canadian General Hospital No. 3 at Wimereux near Boulogne. In January, 1918, Dr. John McCrae, the author of *In Flanders Fields*, died and Dr. Malloch took his place in charge of the "pneumonia huts."

On November 8, 1918, Capt. T. A. Malloch, No. 3 General Hospital, Canadian A.M.C., was mentioned in despatches from Field Marshall Sir Douglas Haig for gallant and distinguished service in the field.

During 1920-1921, he was a Beit Fellow doing research at St. Bartholomew's Hospital and Queens Square Neurological Hospital. He had become a member of the Royal College of Physicians in August, 1918 and was made a Fellow in 1930.

In December, 1919, Dr. Malloch joined the Osler household at Oxford and stayed there as one of the attending physicians until Sir William's death.

At Lady Osler's request Dr. Malloch became one of the editors of the catalogue raisonné of Dr. Osler's collection of eight thousand rare books. The catalogue was finally printed in 1929 as the *Bibliotheca Osleriana*.

In 1922, Dr. Malloch began practice in Montreal but returned to Oxford for four months to continue work on the catalogue of the Osler library. During this visit he met his future wife, Katharine Elizabeth Abbott, a niece of Dr. Osler. They were married at Philadelphia, May 28, 1924.

Dr. Malloch was appointed Librarian to The New York Academy of Medicine on September 16, 1925 to begin his work on January 1, 1926. When circumstances turned his steps to the library world, he resigned as Demonstrator of Medicine at McGill, Assistant Physician at the Royal Victoria Hospital and Assistant Editor of the *Canadian Medical Association Journal*.

At the time Dr. Malloch assumed duty at the Academy, the library consisted of 135,000 volumes and one of his earliest problems was to arrange for the transfer of these books from 43rd Street to our present building. This great task was accomplished in the short space of four

months without loss or damage of a single volume. During this period the Malloch family resided on Riverside Drive. On May 3, 1927, the family moved to Woodlands near Ardsley, Westchester County.

Soon after the opening of the new building Dr. Malloch and the Committee on Exhibits arranged an exhibit of Early and Later Medical Americana and an excellent catalogue was published.

During Dr. Malloch's incumbency as Librarian, the Academy Library grew to be the second largest medical library in the country, with 262,000 volumes, and serving more readers than any other medical library. The staff increased from ten in 1925 to over forty-six librarians organized in departments.

Dr. Malloch established the Department of Rare Books and the History of Medicine, which during his term acquired the Streeter collection and many other important additions, including the latest, the Edwin Smith Surgical Papyrus. He was largely responsible for rousing the interest of Dr. Fenwick Beekman, through whose efforts that valuable accession was acquired.

It was his collaboration with the late Dr. Samuel W. Lambert which led to the formation of the Library Publication Fund which has been an important factor in making the Academy better known in the library world. His interest and influence played a large part in the formation of the "Friends" of the Rare Book Room of the Library of The New York Academy of Medicine.

Dr. Malloch was the author of four books: *Finch and Baines*, 1917, *William Harvey*, 1929, *Short Years: the Life and Letters of John Bruce MacCallum*, 1938, and *Medical Interchange Between the British Isles and America Before 1801*. This last book was an expansion of the two FitzPatrick Lectures which were to have been delivered at the Royal College of Physicians of London in November, 1939, but World War II made this impossible. Dr. Malloch also wrote numerous papers on clinical medicine, medical history, bibliography and biography.

As President from 1927 to 1929, he rendered great service to the Medical Library Association and later became Chairman of the Publication Committee. He served as an honorary consultant to the Army Medical Library and as a consulting editor to the *Journal of the History of Medicine and Allied Sciences*. For many years he was an officer of the British Bibliographical Society.

Dr. Malloch was a member of the Century Association and the Charaka Club. After joining the Charaka Club in 1926 he acted for many years as secretary and as editor of the *Proceedings*.

Summer vacations were spent at Waquoit on Cape Cod where his wife's family, the Abbotts, had been established for many years. Here in a house overlooking the Bay he enjoyed the company of his devoted family and a few close friends who spent their summers nearby.

Dr. Malloch's life was that of a scholar and bookman. His own library reflected his wide interest not only in medicine but in general history and literature. For recreation he enjoyed golf and walking. He was fond of making things out of wood.

With his rare charm and quiet humor he endeared himself to people of all ages and all walks of life. He earned the confidence and affection of the library staff. He was always helpful to others, especially the young. His colleagues recognized his integrity and his learning. His memory will endure in the hearts of students of medical history.

Dr. Malloch is survived by his wife, a daughter and two sons.

CLAUDE EDWIN HEATON

NEW YORK PATHOLOGICAL SOCIETY

*Abstracts of Papers**

Presented at the Meeting, May 21, 1953, at The New York Academy of Medicine

Malignant Mixed Tumors of Major Salivary Glands

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During a 20-year period ending in 1949 there were, at Memorial Hospital, nearly 900 patients with tumors that arose in the major salivary glands. As expected, the majority were classified as benign mixed tumors, there being 494, or 56 per cent, of this type. Fifty-seven were classified as malignant mixed tumors, and, insofar as we know, this represents the only single concentration of tumors of this nature large enough for a reasonably satisfactory group analysis. In order for a tumor to be classified as a malignant mixed tumor there were two requirements,—1) that sections reveal areas having histologic structural qualities found in ordinary mixed tumors; and 2) that the tumor contain areas of different structural make-up which, by experience gained from studying clinical behavior, were known to be associated with the ability to metastasize.

To claim a holding of fifty-seven malignant mixed tumors of major salivary glands may understandably raise the spirit of doubt in the listener. Even now some pathologists, and indeed, clinicians deny the actual existence of malignant mixed tumors of salivary origin. As recently as 1940, Patey[1] stated that he did not know of a reported case in which the evidence was complete that carcinoma had developed from a mixed tumor. Whereas this appears too strong a view in the negative, it must be acknowledged that the literature even to the present is extremely sparse in acceptable cases. The vast majority of tumors reported as malignant mixed certainly belong in other histologic categories. Most of the reported cases are in fact examples of adenoid cystic carcinoma, a distinctly separate type. Largely explanatory for the relatively large numbers of cases claimed at Memorial Hospital has been the concerted emphasis in making extensive pathologic investigations to establish in an obviously malignant-looking tumor the presence of identifiable structures typifying the ordinary benign mixed tumor. It must be borne in mind that many malignant mixed tumors are quite bulky and the malignant overgrowth is commonly very diffuse. Routine sectioning will often fail to reveal limited benign areas and many malignant mixed tumors have for this reason simply been classified as some sort of carcinoma. For many years the laboratory has accented efforts in this direction with the result presently to be described. As one might predict, malignant mixed tumors are much more common in the parotid salivary gland. Here they are four times as frequent as in the submaxillary and we have no such tumor of sub-

* Manuscript received October 1953.

lingual origin. The gross pathologic traits of these tumors were demonstrated in lantern slides. These malignant mixed tumors have few rivals in the diversification of their microscopic make-up. The range of structural variation is too broad to present totally, but several cases were selected which demonstrated most of the structural complexities encountered.

To summarize, malignant mixed tumors may show growth tendencies along the lines of adenocarcinoma which may be tubular or solid; there may be the pattern of epidermoid or squamous carcinoma, malignant spindle cell change or combined spindle and giant cell alteration. The most frequent patterns found in malignant tumors are those of adenocarcinoma and epidermoid carcinoma, and these are often seen in combination. Only occasionally does the sarcomatoid type of growth predominate.

To summarize some of the aspects of the natural history of malignant mixed tumors:

Females predominated in the ratio of 3 to 2.

The median age of patients on hospital admission was fifty-three and extremes of fifteen and seventy-seven were noted. As a group these patients averaged about ten years older than those with benign mixed tumors. This to our mind supports the view that malignant transformation does occur in some mixed tumors that are initially benign and that the advice of McFarland[2] to let mixed tumors lie untouched until they ripen is a poor way to harvest a clean crop of mixed tumors.

The most typical clinical history associated with malignant mixed tumors is one in which the patient has been aware of a mass for several or many years. Most characteristically she or he states that for years the growth was essentially stationary, but within recent months or within the year there was a reactivation with a rate of growth sufficient to cause a three to four times enlargement. On the other hand, the patient may accidentally discover a lump which under observation progressively enlarges either slowly or rapidly. It is, indeed, rare to find a malignant mixed tumor that was quiescent at the time of its removal. Due to these more aggressive growth traits it is understandable that patients with malignant mixed tumors have more frequent and more intense local pain than those with the benign variety.

Malignant mixed tumors even when very large often do not exhibit deep fixation. Invasion of skin does occasionally occur and sometimes in long-standing cases ulceration and hemorrhage supervene. In primary untreated cases facial nerve palsy was a rare clinical finding. Evidence of regional lymph node involvement is seldom found in primary presentations, but was discovered in one-third of the patients with recurrent tumors.

The clinical course of these patients after treatment which was almost entirely surgical was widely variable. A few expired within a year. Local recurrence was common —nearly 50 per cent, and in some cases these recurrences were repeated. During the course of clinical observation nearly 40 per cent developed distant metastases, the evidence being variously based on x-ray, biopsy and postmortem findings. Sites of distant metastases in descending frequency were lungs, bone, abdominal viscera and brain. The time of development of these distant metastases covered a broad period from a few months to many years.

In thirty-three patients followed five years or longer only 48.4 per cent were clinically free from evidence of their disease.

To conclude, it is hoped that the pathologic and clinical material presented is sufficient for accepting the concept of malignant variants of mixed tumors and that aggressive local surgical measures are justified in attempting their control.

Acinic-Cell Adenocarcinoma of Major Salivary Glands: Report of 27 Cases

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The purpose of this paper is to record the clinico-pathologic features of twenty-seven cases of acinic-cell adenocarcinoma encountered in a study of nearly 900 major salivary gland tumors. All but five of these patients were treated at Memorial Hospital.

Heretofore, this tumor has been mentioned only rarely in the literature and then usually as adenoma. However, it is our belief that its clinical behavior warrants its designation as a malignant tumor.

The term "acinic" is employed because of the apparent origin from the serous cells of the acini of the parotid gland. Up to this time the tumor has been found only in the parotid gland, though we anticipate its occurrence in other salivary glands.

Clinically, the lesion simulates mixed tumors of the parotid. The time elapsed between discovery of the lesion by the patient and definitive medical care has varied from a few weeks to sixteen years. Of the twenty-two cases treated at Memorial Hospital, fifteen, or 68 per cent, were in females. The age range from the date of onset of symptoms was seventeen to sixty-eight years. There were nine cases between seventeen and thirty-three years of age, three cases between forty-three and forty-six years, and ten cases between fifty-one and sixty-eight years.

Fourteen patients had received prior therapy. Treatment at Memorial Hospital consisted of excision only in nine instances; excision plus irradiation in six cases, and excision with neck dissection in seven cases. Fifteen of the patients treated at Memorial Hospital are living without disease at present, although several of these for less than five years, so that proper evaluation is not possible. One patient died without apparent residual disease, two died with disease twenty-four and eight years after initial treatment, three are living with disease, and one is indeterminate. Metastases occurred in the two dying of disease. One had subcutaneous metastases and in the other there was spread to the lungs and bones. Metastases to the lung have occurred in one case presently living and in a second case treated elsewhere by Dr. Ashbel Williams. No lymph node metastases have been encountered. The facial nerve has not been impaired in the primary cases, but has been in some of the recurrent ones.

Recurrence has been a common feature, having been encountered in twelve patients. Many of these had several recurrent lesions at various intervals over long periods.

Macroscopically, the primary lesion may closely simulate a mixed tumor. However, it does not present the cartilaginous or glistening white myxomatous surface so frequently encountered in mixed tumors. It is encapsulated, oval, soft to firm, and on cross section is cellular, greyish to brownish white, distinctly friable, crumbling very easily.

The primary tumors average 2 to 3 cm. in diameter. They are generally solid but cystic and degenerative areas are occasionally encountered. The recurrent tumors may show multiple foci separated by bands of fibrous tissue simulating the features of recurrent mixed tumors.

In view of the belief that these tumors arise from the serous acinic cells, it is evident that the most typical microscopic appearance would be one most nearly approaching these cells. Examination of these tumors reveals them to be composed of cells closely resembling normal serous acinic cells with many containing intracellular granules. Most frequently the tumor is not composed entirely of these cells but contains foci of smaller cells with cytoplasm containing no granules.

† By invitation.

Another characteristic is the presence of areas that appear as spaces. We are not certain what these represent but suspect a secretion. These spaces are a nearly constant feature and of assistance in diagnosis in less characteristic patterns of this tumor.

Multiple variations of pattern and cytology have been encountered such that experience with these variations is required before one could safely classify certain lesions in this group.

An occasional tumor is encountered which is composed of a glandular pattern closely resembling the drawings of a case reported by Masson in 1924.[3] Masson recognized his tumor as arising from the serous cells.

Other varieties include tumors containing a trabecular pattern with little granularity of the cytoplasm, and those which contain prominent lymphoid areas. Rarely a papillary cystic arrangement is observed. In the cases in this series the cells were distinctly granular which has not been the case with a few additional papillary cystic lesions studied, the exact classification of which is not apparent at this time.

The variations of pattern from tumor to tumor may be great as mentioned and certain patterns may present difficulty in proper classification, particularly if the helpful cytoplasmic granules and intercellular spaces are not found to assist in diagnosis.

Glycogen, mucus and fat stains have not been of positive value in studying these tumors. With the periodic acid Schiff stain, the granules of the normal serous acinic cells give a positive reaction. The granulated cells composing the tumors also give this same type of reaction. The non-granulated cells do not stain and thereby resemble the non-staining ductal cells of the normal gland which suggests the possible relationship of these cells to the intercalated duct cells. Where there is material in the intercellular spaces, a weakly positive reaction is obtained with the P. A. S. stain.

In rather extensive sectioning of some of these tumors—approaching serial sections—no mixed tumor elements of areas resembling other types of commonly recognized salivary gland tumors have been encountered.

Up to this time lymph node metastases have not been observed. Heretofore, the rather innocuous histologic appearance of the primary tumors would mitigate against serious consideration of their metastasizing capabilities. However, we have an example of a metastasis to the lung with a pattern identical with a recurrence of the primary tumor which is composed of well granulated, uniform cells. This certainly supports the contention that these tumors should be designated as adenocarcinoma.

In summary, we have then, a tumor of serous acinic cell origin clinically simulating a mixed tumor, occurring slightly more commonly in females and most frequently in the fourth to the sixth decades. The course generally is long and recurrence frequent. Metastases in lymph nodes have not been encountered, although they have occurred in other organs. Metastasis occurs in instances in which the histologic pattern of the primary lesion would not lead one to expect such a course.

Treatment appears to be excision of the primary tumor with a good margin and an intact capsule. Neck dissection does not appear indicated in view of the absence of nodal metastases in the material.

DISCUSSION

ARTHUR PURDY STOUT: I listened to these two papers with great pleasure, because I have long been interested in this subject, and I know what a tremendous amount of work has gone into their analysis and compilation. I have also been fortunate enough to have seen the manuscript of Dr. Foote's fascicle on tumors of the major salivary glands,[4] and I can assure you that for the first time, when it is actually published, if our benign government ever gets around to doing it, there will be an extremely valuable book of reference on this obscure subject of salivary gland tumors. I never saw a malignant mixed tumor until I went to Stockholm and spent some time at the Radiumhemmet, going over all those cases that Ahlbom[5] reported in his monograph on tumors of the salivary glands. I saw there what I have never seen since, metastases of malignant mixed tumors in which both epithelial elements and cartilaginous elements were present. We have had fifteen malignant mixed tumors of the major salivary

glands recorded in the Laboratory of Surgical Pathology of Columbia University up to October first, 1952, and I have seen, in addition, a few others with metastases, but I never saw anything but the epithelial elements metastasize. I should like to ask Dr. Foote what their experience has been as to the nature of the metastatic involvement of the nodes. He showed a wider variation of the types of change in malignant mixed tumors than we have seen, probably because he has had four times as many examples as we have. I would like to show you momentarily a lantern slide, if I may, which will show you the division of 515 tumors of the major salivary glands. There were 318 benign mixed tumors, and as you will see in a moment, there were in addition to these, fifteen malignant mixed tumors, which is a smaller percentage of malignant to benign than Dr. Foote indicated as their experience at Memorial Hospital. I think he also suggested the probable reason for this. Memorial Hospital, being a cancer hospital, gets a greater number proportionally of malignant tumors. I believe this experience of ours is more nearly the expected experience of a non-cancer hospital. It required a period of forty-six years for us to accumulate the fifteen cases of malignant mixed tumor.

The next slide shows our division of the different varieties of malignant tumors of the salivary gland. We have not called them all by exactly the same names as Dr. Foote, but it is easy to tell that our use of the term "clear cell carcinoma" corresponds with "acinic cell carcinoma," as you can easily gather from the illustrations, just shown us by Dr. Godwin, of the acinic cell carcinoma. These are malignant tumors, and most of them are in the parotid. Two of our clear cell carcinomas were in the submaxillary gland. I believe the statement was made that all fifteen of the tumors shown by Dr. Godwin were in the parotid. I have no doubt that they do come from the cells of the acini of the salivary gland, and "acinic cell tumor" is probably properly descriptive. It dismayed me a little, because I am not accustomed to the word "acinic." I was assured before the meeting tonight that it is a good dictionary word. It is just unknown to me. I recently had an experience of sending a paper to be published in *The Journal of Thoracic Surgery* in which the word "carina" was used, and I was somewhat astonished to find, when the galley proof came back, that the spelling was changed to "coryna." I went to two dictionaries and I could not find "coryna" in that way, and wrote back and asked how come? I was told that Dr. Evarts Graham had changed the spelling, and they quoted me a dictionary in which it was used. I urged them, if they were going to make me spell it "coryna" to put after it in brackets "carina tracheae," so that the average person would know what it meant. Dr. Godwin has made it clear that "acinic" means derived from the clear cells of the acini.

I would like to mention one more type of carcinoma, or tumor, let us say, which I think may be a carcinoma, but I am not sure. This we have called a papillary carcinoma. When I read Dr. Foote's fascicle, in his descriptive text he spoke about the papillary form of the acinic cell carcinoma, and I thought he was referring to what we were calling papillary carcinomas, but Dr. Godwin's last illustration showing the papillary form of clear cell carcinoma is quite different from this tumor. This lantern slide shows what I mean by the papillary carcinoma. I know that although it is not in his fascicle, Dr. Foote has some cases of this sort, because he told me so just before the meeting, and I do not think, if I understood him correctly, that he believes they are related to the acinic cell carcinoma. I have been wondering, since we have four cases of this sort, and we do not know that any of them metastasized, whether or not this is a malignant tumor. We are keeping it in our classification of malignant tumors simply because someone in St. Louis told me of a case he knew about which looked like this which had metastasized. I am waiting for better evidence than that before reaching a decision.

It has been a great pleasure to hear these two papers, which I think are splendid and clarifying. I would leave you with one more word, however. Even if one spends as much time in studying and classifying salivary gland tumors as Dr. Foote has done, I think one sometimes will be puzzled still

when confronted with a biopsy of a salivary gland tumor. I know I am.

ALFRED ANGRIST: We can all derive considerable comfort from the last remark of Dr. Stout. I am doubtful that Dr. Foote has such difficulty though.

ADOLF HOCHWALD (by invitation): I am unprepared to comment on the cases described by Dr. Foote, and I cannot give statistical data on the material seen at University Hospital of New York University. I recall, however, that in the last half year we have seen a few cases that belong in the categories discussed tonight. First, the acinic cell, or clear cell carcinoma which Dr. Godwin discussed: He mentioned that he never found regional lymph node metastases. We had one case in which a microscopic lymph node metastasis was found. We obtained this specimen because of the procedure of our Tumor Service to carry out routinely a dissection of the cervical lymph nodes in all cases of malignant disease of head or neck, even if lymph node involvement is not manifest clinically.

The second group of cases which we saw recently was the papillary carcinoma of the type mentioned by Dr. Stout. We saw two cases; in both, we had evidence of cervical lymph node metastasis.

FRANK WILLIAM FOOTE, JR.: I know it is a little insubordinate to attempt to correct a president, but I think it is required in this case to state yes, we do have our difficulties from time to time in classifying salivary gland tumors, and I think we shall continue to have these occasional difficulties.

ALFRED ANGRIST: I would be interested to know how many of the frank mixed tumors show squamous areas, i.e., what percentage do,—and what percentage show the structure of epidermoid carcinoma in different areas. We have encountered some of these, and I wonder how often that combination occurs. Also do you ever encounter cylindromas in your mixed tumor material?

We have another notion for correction; it has been my experience that when these salivary tumors do metastasize, even though they may occasionally metastasize distantly, that ordinarily the metastases may not be very numerous and widely disseminated. I may be wrong about that, and would want to be corrected. I am comparing them generally with other malignant tumors that do metastasize. They so often tend to be regional and not uncommonly show a solitary metastasis. Is that your experience? We have seen a few cases like that.

I would like to ask Dr. Godwin whether he thinks the acinic cell adenocarcinomas bear any relationship to the oncocytomas or the more common manifestations of like cells in lymph nodes, and how one would differentiate such elements from a metastatic focus, when one is confronted with them in that situation.

FRANK WILLIAM FOOTE, JR.: I am not sure that I can remember every one of these questions in its correct order, but we started on squamous areas. As I recall our statistical sheet on squamous metaplasia in the benign group, the figure 25 per cent sticks in my mind. Any figure we gave would be subject to correction. It would depend on how many blocks were embedded for study. In the malignant variants we found tendencies toward epidermoid or squamous differentiation in about half the cases. People vary in what they are willing to report as epidermoid differentiation. I am rather liberal myself. Such figures will run up and down, depending on the individual observer.

Dr. Angrist mentioned the metastatic pattern. I can state in confirmation of his experience that there are cases in which the metastatic pattern is relatively limited, say a few large deposits in lungs. We had, however, a number of tumors that did generalize widely to multiple viscera and bones. We do not have as much material from metastatic lesions as we would like, so I feel hesitant about making detailed statements about the microscopic appearance of metastases.

Harking back to Dr. Stout's remarks, our material did not contain mixed tumor metastases with cartilaginous components. We had an opportunity of studying a very interest-

ing case published by Perrin in 1942.[6] This case was reported as a metastasizing mixed tumor without the histologic structure of frank carcinoma. I secured permission to look at and comment on the material. The feature of this case of particular interest was that the primary and metastatic tumors had both epithelial and connective tissue-like components, not cartilage, but a spindle cell matrix, benign looking with epithelial aggregates that to us looked malignant. Perrin later wrote and said that for some time he had felt uncertain about the case and finally considered that he had a cylindroma in which there was a peculiar spindle cell stroma.

I might expand further on cartilaginous material in mixed tumor metastases. The case to be mentioned has not as yet been reported. It came to our attention after we had finished the fascicle to which Dr. Stout generously alluded. We were so tired of salivary gland tumors that we did not feel like opening the page again. Dr. William Watson in 1937 first operated on Selma B. who at that time had an already twice recurrent parotid mixed tumor. During the next nine years three more local recurrences were excised, the last in 1946. For seven years almost to the day she remained free of tumor. In 1953 she returned to the hospital and showed a rounded density in the left lower lobe. We gave Dr. Watson every assurance that this was not related to the prior existing benign-looking mixed tumor. We could find no conclusive report of a metastasis from a histologically benign mixed tumor. A partial lobectomy was done and the little nodule proved to be an every-day, run of the mine benign-looking mixed tumor. It had a distinct chondroid matrix, and it looked like the previous material from the many local excisions from the parotid area.

JOHN T. GODWIN: I do not believe there should be any great difficulty in differentiating the oxyphilic granular cell adenoma or oncocytoma that Dr. Angrist has mentioned. I think the slide shows very clearly a fairly typical oxyphilic granular cell adenoma and you can see the difference between this section and the previous one concerning the acinic cell tumors. These cells are fairly large and have relatively uniform nuclei, and an eosinophilic cytoplasm which is very finely granular. It has been shown in recent years, in 1949, in an article in The American Journal of Pathology, by Meza-Chávez,[7] that some of these tumors do arise from the acini or from some of the cells contiguous to the acini, but I believe that these tumors should be definitely differentiated.

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Jaundice in Hodgkin's Disease

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Jaundice is not rare in Hodgkin's disease. The average incidence according to the literature ranges from 3 to 8 per cent.[1-6] When patients with widespread Hodgkin's disease develop jaundice, and after the obvious causes of jaundice, such as transfusion reactions, are ruled out, most clinicians ascribe the icterus to obstruction by compression or obliteration of the extrahepatic biliary ducts by Hodgkin's tissue. We undertook this study to confirm or deny this prevailing concept of jaundice in Hodgkin's disease.

Although the role of obstruction is generally conceded to be the important one, several other jaundice-producing diseases which may be associated with Hodgkin's disease must be considered as well as all coincidental entities that produce jaundice. The former group includes viral hepatitis, important because of the increased exposure to this disease which patients with Hodgkin's disease undergo when they receive large quantities of transfused blood or are intentionally inoculated with the virus of hepatitis as a therapeutic procedure as suggested and carried out by Hoster[7] (1949) after he had observed long remissions in patients with Hodgkin's disease who contracted viral hepatitis.

The second associated entity is that of hemolytic anemia. Aside from the normally occurring hemolysis of transfused blood (20 per cent), and that occurring in transfusion reactions, a distinct complicating hemolytic anemia syndrome has been described in Hodgkin's disease by Dameshek and others.[8-9] This has been classified by some as secondary hypersplenism. The spleen in these cases is generally involved by Hodgkin's disease. The mechanism of increased blood destruction is obscure. However, increased osmotic fragility is the rule and spherocytosis may be demonstrated.

The above modalities have been dismissed because: 1) No evidence of acute viral hepatitis was found in our studied material; and 2) clinical evidence supporting any hemolytic pathogenesis of jaundice in our cases was absent.

Our main consideration, therefore, will be jaundice produced by the obstructive mechanisms of Hodgkin's disease. Coronini, cited by Wallhauser[2] in 1928, outlined the following mechanisms of jaundice in Hodgkin's disease, all of which are obstructive in nature:

1. Obliteration of the common duct alone.
2. Compression of the common duct alone.
3. Changes in both the extra- and intrahepatic ducts.
4. Changes limited to the intrahepatic ducts.

Opinion concerning the site of obstruction is divided; the current consensus would seem to favor the extrahepatic mechanisms. Symmers,[1] although favoring the extrahepatic genesis, describes jaundice in cases showing only intrahepatic duct obstruction by the lesions of Hodgkin's disease. It was Barron[3] in 1926 who stated, "It is likely that peribiliary infiltration produces jaundice more frequently than does pressure by enlarged lymph nodes or tumor masses against the large bile ducts." This variation on the emphasis has served as an additional stimulus for this study in the hope of adding some weight to one or the other side. The terminology used by us is that outlined by Jackson and Parker,[10] viz, Hodgkin's paragranuloma (no cases), Hodgkin's granuloma and Hodgkin's sarcoma.

For this study we selected forty cases of Hodgkin's disease coming to autopsy at the Memorial Center for Cancer and Allied Diseases within the past five years. Twenty-

three of the forty patients were jaundiced at death and sixteen of these had Hodgkin's granuloma with liver involvement; three had Hodgkin's sarcoma with liver involvement by Hodgkin's disease. Sixteen cases serving as controls were not jaundiced, but had Hodgkin's disease in their livers. In one non-icteric Hodgkin's case there was no involvement with hepatic Hodgkin's disease but massive hepatic amyloidosis which will be discussed later.

On examining the gross autopsy protocols in our jaundice cases, which include the latter two types of Hodgkin's disease, in only two was the jaundice considered to be due to extrahepatic obstruction. There was obstruction by paracholodochal lymph nodes in one instance and obstruction at the porta hepatis in the other. However, in none of our cases presenting jaundice was there microscopic evidence of extrahepatic obstruction such as intrahepatic duct dilatation, biliary cirrhosis or both. Bile thrombi were present in the terminal canaliculi in our most severely jaundiced cases, however. Lacking evidence to support the extrahepatic obstructive theory we attempted to find a common denominator in the livers of the jaundiced patients having liver involvement as compared with liver involvement by Hodgkin's disease in patients without jaundice.

The granuloma group will be discussed first.

In this group the males were predominantly affected with regard to the liver; this observation is consistent with the sex incidence of Hodgkin's granuloma as a whole, 1.9/1. What is more interesting is the male dominance in the jaundiced patients with Hodgkin's granuloma, 4.3/1.

Our microscopic findings in Hodgkin's granuloma involving the liver, with and without jaundice, are as follows:

In all sixteen cases of jaundice, practically all of the portal triads were involved by Hodgkin's granuloma and fibrosis of the Hodgkin's tissue was marked. The degree of fibrosis of Hodgkin's tissue in other organs as compared with the liver has not been assessed. The size of the nodules per se apparently played no significant part in the production of jaundice. In thirteen cases in which there was no jaundice, there occurred either one of these changes, i.e., fibrosis or the diffuse periportal localization of Hodgkin's disease—but not both. In cases showing marked fibrosis, many portal trinities were uninvolved by Hodgkin's disease. In those showing diffuse periportal involvement, fibrosis was absent or minimal.

The above observations do not apply to the cases of Hodgkin's sarcoma. In the six cases of Hodgkin's sarcoma, the sex incidence is 1:1. The small number of the cases studied precludes anything but a superficial and speculative conclusion regarding the etiology of jaundice in the group. One difference was noted, however. In the three non-jaundiced patients with Hodgkin's sarcoma, the intervening liver tissue was relatively intact, while in the three jaundiced ones, the liver tissue was necrotic. The etiology of the necrosis is obscure, but hepatotoxic drugs and disturbances in liver circulation must be considered.

Of the remaining five miscellaneous cases, the instance of hepatic amyloidosis is included because of jaundice in the patient which occurred several months before death but subsequently cleared. Although massive diffuse hepatic amyloidosis may produce jaundice, it is rare, and the etiology of the earlier jaundice in this case cannot be determined.

Of the remaining four miscellaneous cases in which there was jaundice without liver involvement by Hodgkin's disease, the patient with posthepatitic cirrhosis had been nonicteric until four months before death when he developed a classic case of viral hepatitis. He remained jaundiced until death.

The finding of massive centrilobular congestion and necrosis in one case suggested distal venous obstruction, although this feature could not be demonstrated at autopsy.

In two cases there was no gross or microscopic evidence of liver disease although there had been mild jaundice which appeared twenty-four hours prior to death in the one case and forty-eight hours before death in the other. No anatomic cause, including unrelated exogenous causes, could be found.

From our study we would like to submit the following conclusions:

1. Obstruction of the extrahepatic biliary ducts played no demonstrable part in the production of jaundice in the cases studied and, on this basis, it would appear to be, at most, an infrequent cause.

2. Patients with jaundice showing liver involvement by Hodgkin's granuloma, demonstrated diffuse involvement of the portal trinities with fibrotic Hodgkin's disease.

3. Non-jaundiced patients with liver involvement by Hodgkin's granuloma did not show this complex.

4. In patients with liver involvement with Hodgkin's sarcoma the etiology of jaundice is not clear, but intervening liver necrosis in the cases with jaundice was demonstrated, while it was absent in the non-jaundiced patients.

5. Patients developing jaundice immediately prior to death may show no histologic evidence of liver disease.

It is certain that there are exceptions to this over-all thesis. Borderline qualitative and quantitative changes with regard to considering a case as one of jaundice from the study of the liver sections alone will be seen, and in any given case multiple causal factors may be operative, or no cause found. This study is presented to stimulate re-evaluation of the older concepts regarding the genesis of jaundice in Hodgkin's disease.

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DISCUSSION

ALFRED ANGRIST: I have encountered several cases of jaundice with extrahepatic occlusion by Hodgkin's disease, and I wonder whether others have not had the same experience.

DOUGLAS SUNDERLAND (by invitation): I should like to ask Dr. Beatty if, in his jaundiced patients with Hodgkin's granuloma with marked fibrosis, he found any correlation with ascites.

ARTHUR C. ALLEN: In those cases you just referred to, Dr. Angrist, of extrahepatic obstruction by nodes, I wonder if there was intrahepatic involvement causing the jaundice.

ALFRED ANGRIST: Yes, but the impression was that the jaundice was caused by stenosis of the larger ducts. I know this does occur, and I wonder what Dr. Beatty's experience has been. One of the explanations offered, at least by myself, in explaining the failure of dilatation to occur proximal to the obstructive lesion in the duct, has been that the fibrosis has extended along the duct structures and that this has prevented the dilatation. The jaundice that appears in these cases does not last as long clinically as is the common story of obstructive jaundice as it occurs in carcinoma of the head of the pancreas. At least it has been my experience that the jaundice in Hodgkin's disease is a pretty lethal symptom. I wonder what the duration and extent of the jaundice was in the group of cases presented. In cases where the extrahepatic or larger intrahepatic ducts are involved, it is a progressive, inevitable, continuing jaundice of the Courvoisier's type, and I wonder whether that was the finding in this series of cases.

THOMAS G. MORRIONE: I wonder whether Dr. Beatty did reticulum stains on these livers. The reason I ask is that I believe that one is better able to judge the degree of fibrosis by the reticulum stain, especially if one combines it with the trichrome stain. One may arbitrarily define the degree of fibrosis as that which is detectable or visible with the H and E stain, but in

the past we found this method unsatisfactory. In attempting to correlate the histologic grading (*zero* to *four* plus) of fibrosis in cirrhotic livers with quantitative chemical collagen data, the two sets of data did not coincide well at all. Even trichrome-stained preparations did not enable us to accurately predict the collagen content. It was only when we used the reticulum stain that we were able to obtain very good correlation between our grading of the degree of fibrosis (accepting reticulum as collagen, as most people will) and the chemical data. I do not mean to imply that Dr. Beatty's conclusions would necessarily be different, but I would feel a little more satisfied about the accuracy of the grading of the fibrosis.

EDITH E. SPROUL: Dr. Beatty mentioned very briefly that he thought some of the therapeutic agents he mentioned in Hodgkin's disease might have been injurious to the liver. I wonder if he will speak about that.

ALFRED ANGRIST: If the summation of such focal intrahepatic involvement in the biliary triads is effective on an obstructive basis, why don't we see more often bile casts in the terminal canaliculi? It has been my impression that they do not occur very often in relation to intrahepatic Hodgkin's, although I have not made a directed survey of this.

There are still other mechanisms of jaundice that can apply. It is not at all uncommon, and I imagine you eliminated this type of case from your group, to see a patient with Hodgkin's disease, like lymphosarcoma, develop a rapid anemia, undoubtedly on the basis of hemolysis, which can contribute to overburdening a liver, not too well because of the severe illness of the patient, and thus contribute to the jaundice, so that some of the jaundice clearly has a distinct biochemical mechanism, and this factor cannot be explained on the basis of the morphologic criteria. I suspect that these biochemical and toxic factors may account for some of the cases you referred to in which you did not find exact correlation between the morphologic involvement and the degree of jaundice.

EUGENE C. BEATTY, JR.: The answer to Dr. Sunderland's question on the problem of ascites and peripheral edema is complicated by the fact that the illness of the patient is terminal, usually with low serum proteins. However, in these cases there was a high degree of correlation of the ascites at death.

Dr. Angrist's two questions; first of all, the problem of bile casts. It has been suggested that they may be correlated with the degree of jaundice in the patient, and in our cases generally the jaundice was of low grade, most of them running under 10, using bilirubin as the criterion for the degree of jaundice, and perhaps for that reason, the mildness of the jaundice in many cases would preclude the formation of bile thrombi in the terminal canaliculi. As for the rapidly developing anemia in some of these cases, perhaps these would fall into the group of secondary hypersplenism with increased erythrocyte fragility.

In answer to Dr. Sproul's question, the hepatotoxic drug I was referring to chiefly was nitrogen mustard, and the evidence for that is somewhat equivocal. However, I believe that Dameshek and some other workers gave nitrogen mustards to experimental animals and also studied autopsy material at various times after the drug had been given, and were able to observe that they did attack the liver by producing a polymorphonuclear infiltrate in the parenchyma shortly after the drugs were given, and then produced subsequent necrosis of liver tissue which was apparently maximal at about nineteen days. Then his material, in time, jumped a long span, so that after fifty-eight days had elapsed he was able to determine that the liver had pretty well regenerated and he suggested that perhaps the nitrogen mustard given to a patient with a relatively intact liver would not produce any serious damage, but perhaps in the overburdened liver, the nitrogen mustard added enough damage to the liver with the subsequent manifestation of jaundice in the patient.

As for the reticulum stain, we did not do reticulum or trichrome stains, Dr. Morrione, so I cannot answer your question about the correlation.

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LIBRARY NOTES

SECOND SUPPLEMENTAL LIST OF AVAILABLE PUBLICATIONS[1]

HEREDITY IN HEALTH AND MENTAL DISORDER by Franz Josef Kallmann. N. Y.: Norton [1953], 315 p. (Salmon Memorial Lecture, New York Academy of Medicine, 1952.) Obtain from publisher. $6.00

STREPTOCOCCAL INFECTIONS. Ed. by Maclyn McCarty. N. Y.: Columbia Univ. Press. (The New York Academy of Medicine, Section on Microbiology, Symposia, No. 7.) 1954, 219 p. $5.00

NEW YORK ACADEMY OF MEDICINE, 25th Graduate Fortnight, 1952: Hormones in Health and Disease. Ed. by Robert L. Craig, N. Y.: Macmillan. In Press. $6.50

BEYOND THE GERM THEORY. N. Y.: Health Education Council. (The Eastern States Health Education Conference, 1952.) Issued by the Committee on Medical Information. In Press

TRANSACTIONS OF THE CONFERENCE ON MINISTRY AND MEDICINE. N. Y.: International Universities Press. Issued by the Committee on Medical Information. In Press

LECTURES TO THE LAITY—1950/51 and 1951/52. N. Y.: International Universities Press. Issued by the Committee on Medical Information. In Press

LECTURES TO THE LAITY—1952/53. N. Y.: International Universities Press. Issued by the Committee on Medical Information. In Press

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1 Original list of "Available Publications" published in the *Bulletin of The New York Academy of Medicine*, n.s.*28*:53-58, 1952. The "Supplemental List of Available Publications" published in the *Bulletin of The New York Academy of Medicine, n.s.29*:577, 1953.

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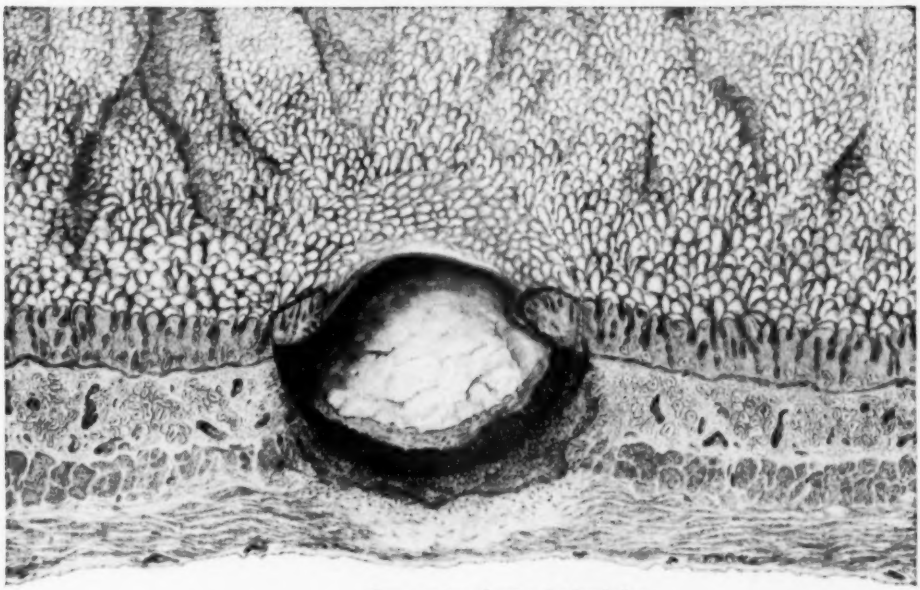

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1. Ruffin, J. M.; Baylin, G. J.; Legerton, C. W., Jr., and Texter, E. C., Jr.: Mechanism of Pain in Peptic Ulcer, Gastroenterology *23*:252 (Feb.) 1953.
2. Schwartz, I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: A Clinical Evaluation of a New Anticholinergic Drug, Pro-Banthine, Gastroenterology *25*:416 (Nov.) 1953.

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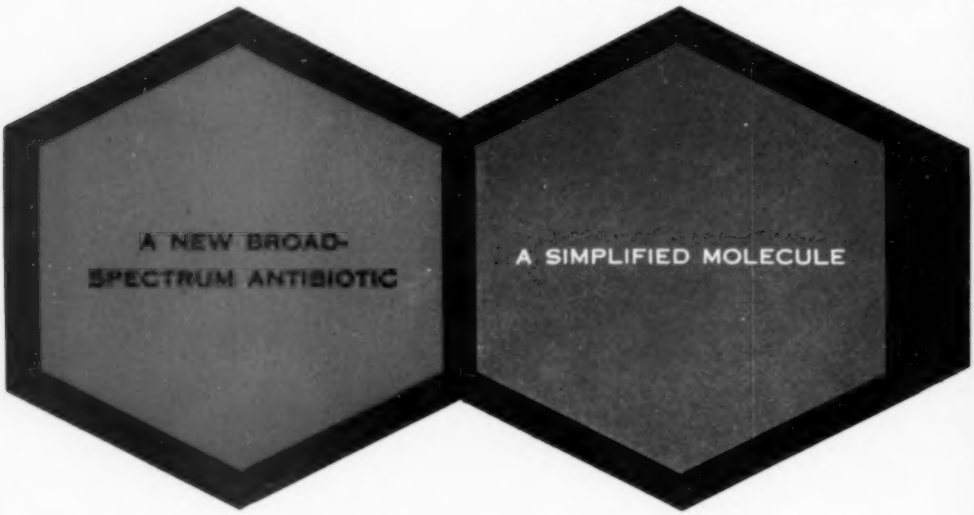

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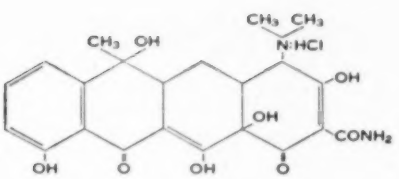

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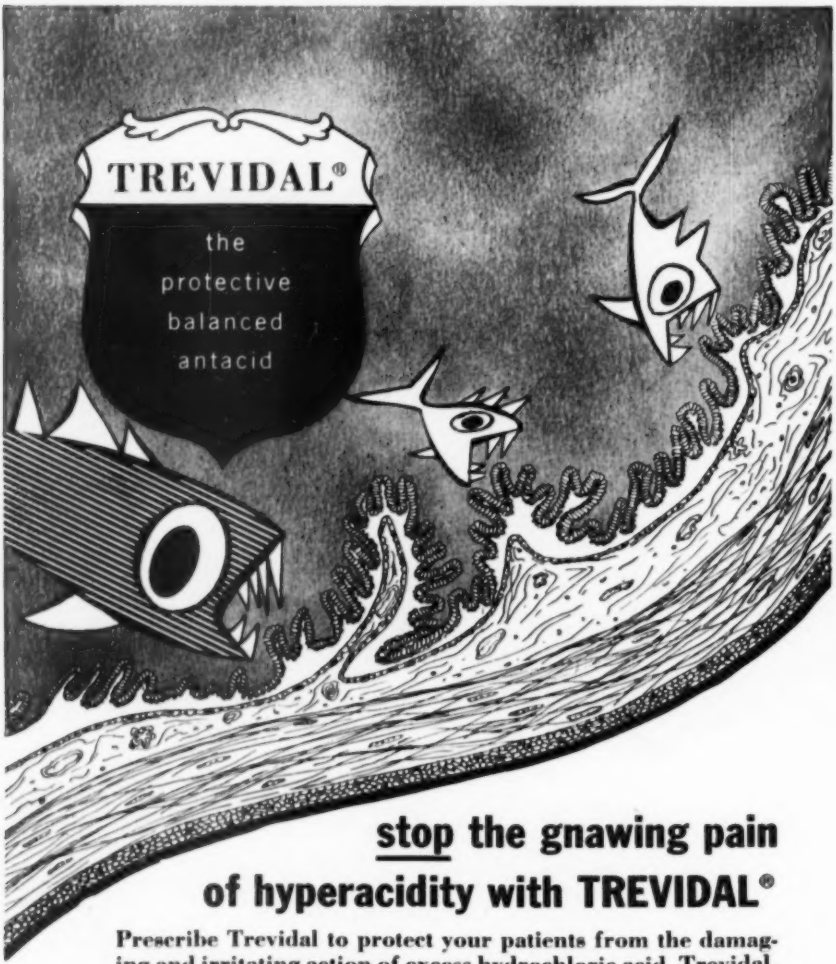

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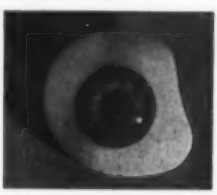

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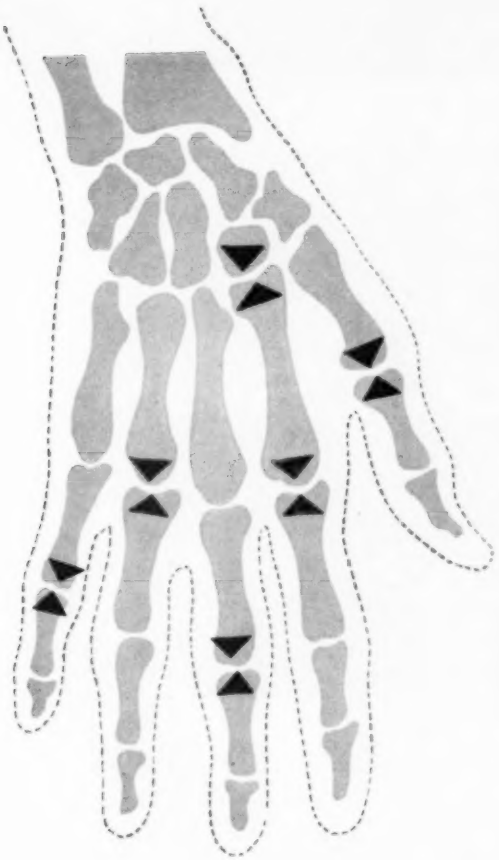

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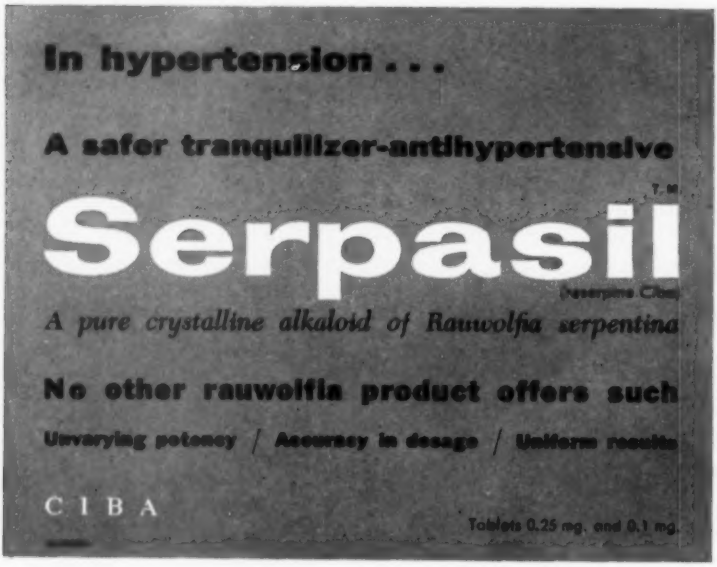
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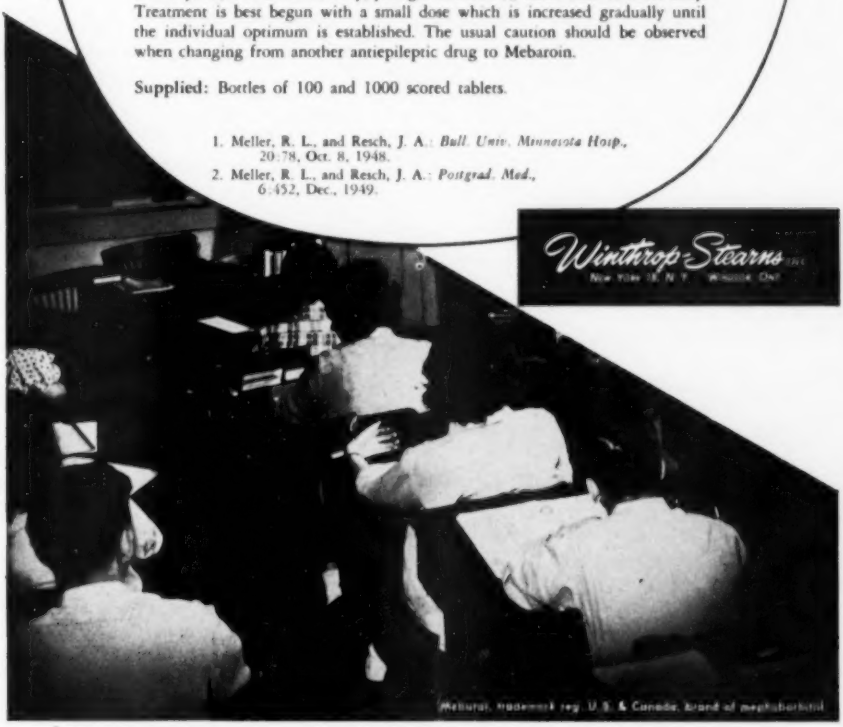
1. Meller, R. L., and Resch, J. A.: *Bull. Univ. Minnesota Hosp.*, 20:78, Oct. 8, 1948.
2. Meller, R. L., and Resch, J. A.: *Postgrad. Med.*, 6:452, Dec., 1949.



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1. Greenblatt, R. B., and Kupperman, H. S.: M. Clin. North America *30*:576 (May) 1946. 2. McGavack, T. H., in Goldzieher, M. A., and Goldzieher, J. W.: Endocrine Treatment in General Practice, New York, Springer Publishing Company, Inc., 1953, p. 225.

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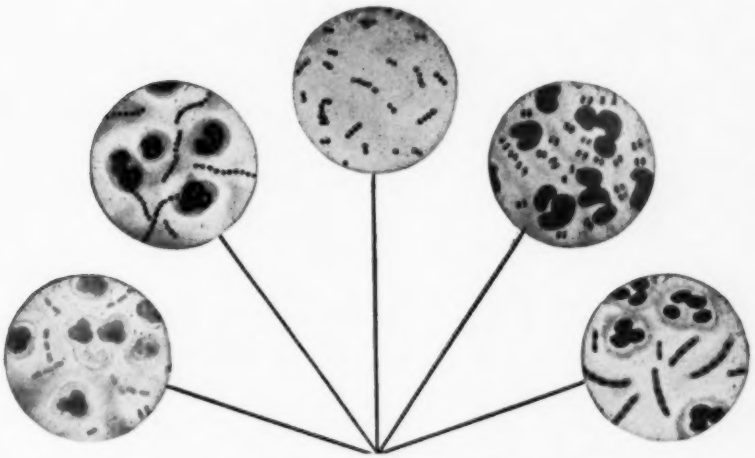

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1. Kolmer, J. A., and Rule, A. M.: Am. J. Med. Sc. *215*:136-148 (Feb.) 1948
2. Lehr, D.: Antibiot. & Chem. *3*:89 (Jan.) 1953

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